7. SLOVENSKI ENDOKRINOLOŠKI KONGRES

Bled
20.–22. oktober 2022

ZDRUŽENJE ENDOKRINOLOGOV SLOVENIJE

ZBORNIK PREDAVANJ IN IZVLEČKOV PROSTIH TEM

BOOK OF PROCEEDINGS AND ABSTRACTS

7. slovenski endokrinološki kongres

ZBORNIK PREDAVANJ IN IZVLEČKOV PROSTIH TEM

7th Slovenian Congress of Endocrinology

BOOK OF PROCEEDINGS AND ABSTRACTS

Uredniki: Katica Bajuk Studen, Aleš Skvarča, Katarina Mlekuš Kozamernik
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SLOVENSKO OSTEOLOŠKO DRUŠTVO

7. slovenski endokrinološki kongres

z mednarodno udeležbo

Zbornik predavanj in izvlečkov prostih tem

7th Slovenian Congress of Endocrinology

Book of Proceedings and Abstracts

Rikli Balance Hotel
Bled, 20.–22. oktober 2022

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NAGOVOR
GREETING

Spoštovane kolegice in spoštovani kolegi, drage prijateljice in dragi prijatelji,

v veliko veselje in čast mi je, da vas lahko v imenu Programsko-organizacijskega odbora povabim na 7. slovenski endokrinološki kongres z mednarodno udeležbo, ki bo potekal na Bledu med 20. in 22. oktobrom 2022. Veselim se, da se bomo lahko ponovno srečali, izmenjali izkušnje in se seznanili z najnovejšimi dognanji na področju odrasle in pediatrične endokrinologije, diabetologije in tirologije.

Pripravili smo razgiban in aktualen strokovni program. Že uvod v četrtek bo udaren in ga nikakor ne smete zamuditi, saj se bomo dotaknili večnega vprašanja o reverzibilnosti sladkorne bolezni tipa 2. V nadaljevanju bomo analizirali pristop k obravnavi akromegalije, pediatri pa nam bodo predstavili obete genskega zdravljenja. Petkov strokovni program prinaša obravnavo funkcionalnega hipogonadizma in reproduktivne endokrinologije, prikaz napredka v presejanju na diabetično nogo, osvetlitev 80 let zdravljenja z radiojodom in vpogled v hiter razvoj na področju sodobnih tehnologij pri zdravljenju sladkorne bolezni. Drugi dan kongresa bomo zaključili z vse bolj perečo problematiko karcinoma pankreasa v povezavi z debelostjo in sladkorno boleznijo. Sobotno dopoldne pa bo namenjeno kortizolu in predstavitvi prostih tem. Vse dni kongresa bodo popestrila zelo zanimiva satelitska predavanja naših sponzorjev.

In nenazadnje – dovolj časa bo tudi za druženje in sprostitev. Če česa, nas je čas pandemije naučil, kakšna vrednota so soljudje, tudi kot večno ogledalo nas samih.

Se kmalu vidimo na Bledu!

Aleš Skvarča

Predsednik Združenja endokrinologov Slovenije

Dear colleagues, dear friends,

it is my great pleasure and honour to invite you on behalf of the Program and Organizing Committee to the 7th Slovenian Congress of Endocrinology, which will take place in Bled between October 20th and 22nd, 2022. I look forward to meeting you again, exchanging experiences and getting acquainted with the latest findings in the field of adult and paediatric endocrinology, diabetology and thyroidology.

We have prepared a varied and up-to-date scientific program. The introduction on Thursday will be a hit and should not be missed, as we will touch upon the eternal question of the reversibility of type 2 diabetes. In the following, we will analyze the approach to the acromegaly treatment, and paediatricians will present the prospects of gene therapy. Friday's scientific program brings a discussion of functional hypogonadism, reproductive endocrinology and progress in diabetic foot screening. We will highlight 80 years of radioiodine treatment and give an insight into the rapid development of modern technologies in the treatment of diabetes. We will close the second day of the congress with the critical issue of pancreatic carcinoma related to obesity and diabetes. Saturday morning will be dedicated to cortisol and oral presentations. All three days of the congress will be enriched by the interesting satellite symposia of our sponsors.

And last but not least – there will also be enough time to socialize and relax. If anything, the time of the pandemic has taught us the value of fellow human beings, also as an eternal mirror of ourselves.

See you soon in Bled!

Aleš Skvarča

President of Slovenian Endocrine Society

MAHKOTOVO PRIZNANJE 2022

Prof. dr. Ciril Kržišnik

Slovenska pediatrična endokrinologija je pogumno stopila na samostojno pot v zgodnjih šestdesetih letih po vrnitvi prof. dr. Leva Matajca z izobraževanja v Parizu. Prof. dr. Ciril Kržišnik se je tej samostojni poti pridružil zelo kmalu in jo skoraj od začetka soustvarjal. Z izobraževanj v tujini je postopno prinašal nove ideje, strokovna dognanja in inovativne pristope k obravnavi pediatrične populacije. Ob vse večji prepoznavnosti Slovenije kot strokovne entitete na področju pediatrične endokrinologije mu je uspelo leta 1989 na Bled pripeljati letni svetovni kongres International Society for Pediatric and Adolescent Diabetes (ISPAD, takrat še ISGD), kar je Slovenijo postavilo na mednarodni zemljevid pediatrične endokrinologije.

Na področju zdravljenja z rastnim hormonom je bila Ljubljana med prvimi partnerji v projektu zbiranja človeških kadavrskih hipofiz, iz katerih so potem v Združenih državah Amerike ekstrahirali rastni hormon, katerega del se je kot zdravilo vrnil na našo ustanovo. Po uvedbi rekombinantnerga rastnega hormona pa je Ljubljana postala center za sledenje učinkov zdravljenja v okviru več mednarodnih sledilnih raziskav. Prof. dr. Ciril Kržišnik je kot prvi v Srednji Evropi zdravil otroka z Laronovim sindromom, sodeloval pa je tudi pri uvajanju prvega presejalnega testiranja novorojenčkov, ki ga je pokojni prof. dr. Varl takrat lociral v okvir tirologije.

Osamosvojitev Slovenije je prinesla številne nove strokovne možnosti. Prof. dr. Kržišnik je usmeril Oddelek za endokrinologijo, diabetes in bolezni presnove Pediatrične klinike na pot mednarodne uveljavitve in mladim, ki smo se mu na tej poti pridružili, omogočil izobraževanja v najbolj prestižnih tujih ustanovah. Omogočil je tudi začetek sistematičnega raziskovalnega dela, ki je bilo do njegovega vodstva na Pediatrični kliniki pogosto potisnjeno v ozadje. Ohranil je svoje strokovno zanimanje za bolezni hipofize in s kolegom s Hrvaške

opredelil večjo skupino bolnikov z družinskim panhipopituitarizmom. V sodelovanju z laboratorijem prof. Parksa iz Atlante je opredilil mutacije v genu PROP-1, kar je v devetdesetih letih pomenilo strokovni vrh v endokrinologiji. Vodil je raziskovalne projekte na področjih tirologije in genetike kongenitalne adrenalne hiperplazije, kjer je Ljubljana dobro desetletje v sodelovanju s prof. dr. Vito Dolžan predstavljala regionalni center za genetske analize te bolezni v okviru Srednjeevropskega združenja za pediatrično endokrinologijo. S kolegi je vodil nacionalne registre redkih bolezni in tudi s tem uvrščal Slovenijo med države z urejenimi podatki o redkih boleznih, ki so nas uvrščali v številne zelo odmevne mednarodne publikacije.

Vse te dolgoletne strokovne in raziskovalne aktivnosti so omogočile, da je European Society for Pediatric Endocrinology, naše največje mednarodno strokovno združenje, prof. dr. Kržišnika izvolilo za svojega predsednika in s tem tudi za organizatorja 42. letnega kongresa v Ljubljani leta 2003. To je bil resnični praznik endokrinologije s preko 2500 udeleženci z vsega sveta. Sloves ljubljanske in slovenske pediatrične endokrinologije in s tem endokrinologije nasploh se je, ob sočasnih vidnih uspehih kolegov endokrinologov internistov, tako dejansko razširil na vse najbolj imenitne naslove po svetu.

Prof. dr. Ciril Kržišnik je iz strokovne megle avtoritarne medicine razvil na dokazih temelječo pediatrično endokrinologijo in jo utrdil v strokovnem, raziskovalnem in organizacijskem pogledu. Z mentoriranjem in stalnim spodbujanjem mlajših kolegov pa je ustvaril generacije univerzitetnih učiteljev, ki v novi stavbi Pediatrične klinike, zrasle pod njegovim vodstvom, z veseljem nadaljujemo njegovo delo.

Prof. dr. Tadej Battelino

PROGRAMSKO-ORGANIZACIJSKI ODBOR

PROGRAMME AND ORGANIZING COMMITTEE

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Mojca Jensterle Sever
Tomaž Kocjan
Primož Kotnik
Urša Kšela
Draženka Pongrac Barlovič
Andrej Zavratnik

STROKOVNI PROGRAM

SCIENTIFIC PROGRAMME

Četrtek, 20. oktober 2022

12.00 Registracija in odprtje razstave

13.30–14.30 *Kosilo*

15.00–16.00 **SKLOP 1** **Reverzibilnost sladkorne bolezni tipa 2 – ali je sploh mogoča?**

Moderator: **Draženka Pongrac Barlovič**

- **Funkcionalne spremembe v beta celicah med razvojem in remisijo sladkorne bolezni tipa 2** (Andraž Stožer)
- **Weight loss and type 2 diabetes remission: lessons learned?** (Michael Lean)

16.00–17.00 **SKLOP 2** **Akromegalija – številke ali stol?**

Moderator: **Urša Kšela**

- **Številke** (Tomaž Kocjan)
- **Stol** (Mojca Jensterle Sever)

17.00–17.30 **SATELIT 1** **Srebrni sponzor** (Pfizer)

17.30–18.00 *Odmor*

18.00–18.30 **OTVORITEV KONGRESA**

Mahkotovo priznanje

18.30–19.30 **SKLOP 3** **Obeti genskega zdravljenja**

Moderator: **Mojca Žerjav Tanšek**

- **Genetika nizke rasti** (Jasna Šuput Omladič)
- **Nove oblike zdravljenja ahondroplazije** (Primož Kotnik)
- **Gensko zdravljenje presnovnih bolezni** (Urh Grošelj)

19.30–20.00 **SATELIT 2** **Zlati sponzor** (Abbott)

20.30–21.30 *Večerja*

Petek, 21. oktober 2022

08.30–09.00 **SATELIT 3** **Srebrni sponzor** (Gedeon Richter)

09.00–10.00 **SKLOP 4** **Funkcionalni hipogonadizem: hujšanje ali testosteron?**

Moderator: **Nadan Gregorič**

- **Hujšanje** (Matej Rakuša)
- **Testosteron** (Kristina Groti Antonič)

10.00–10.30 **SKLOP 5** **Presejanje na diabetično nogo: včeraj, danes, jutri**

Moderator: Aleš Pražnikar

- **Presejalni test od leta 1996 do leta 2022: sporočila iz podatkovne baze** (Vilma Urbančič Rovan)
- **Optimizacija presejanja s pomočjo napovednih modelov** (Iztok Štotl)

11.00–11.30 *Odmor*

11.30–12.30 **SKLOP 6** **80 let zdravljenja z radiojodom**

Moderator: **Katica Bajuk Studen**

- **Privzem radiojoda** (Katja Zaletel)
- **Zdravljenje z radiojodom** (Edvard Pirnat)
- **Radiojod in ščitnična orbitopatija** (Polona Jaki Mekjavić)
- **Radiojod pri mladostnikih** (Simona Gaberšček)

12.30–13.30 **SKLOP 7** **Sodobne tehnologije pri zdravljenju sladkorne bolezni**

Moderatorja: **Tadej Battelino, Aleš Skvarča**

- **Glikemija in kakovost življenja z uporabo zaprte zanke pri mladih** (Nataša Bratina)
- **Sodobne tehnologije pri zdravljenju sladkorne bolezni in telesna dejavnost** (Klemen Dovč)
- **Uporaba sodobnih tehnologij v času nosečnosti** (Draženka Pongrac Barlovič)

Petek, 21. oktober 2022

13.30–14.00 **SATELIT 4** **Zlati sponzor** (Novo Nordisk)

14.00–15.00 *Kosilo*

15.00–16.00 **SKLOP 8** **Reproduktivna endokrinologija**

Moderator: **Mojca Jensterle Sever**

- **Vloga GLP-1 v reproduktivnem zdravju žensk** (Vesna Šalamun)
- **Vloga GLP-1 v reproduktivnem zdravju moških** (Nadan Gregorič)
- **Interdisciplinarno obravnavanje neplodnosti: endokrinolog in reproduktivni ginekolog** (Eda Vrtačnik Bokal)

16.00–16.30 **SATELIT 5** **Srebrni sponzor** (Novartis)

16.30–17.00 *Odmor*

17.00–18.00 **SKLOP 9** **Karcinom pankreasa, debelost in sladkorna bolezen**

Moderator: **Andrej Janež**

- **Karcinom pankreasa – podatki iz Slovenskega registra raka** (Vesna Zadnik)
- **Nevarnostni dejavniki, ocena ogroženosti in presejanje bolj ogroženih za raka trebušne slinavke** (Mateja Krajc)

18.00–19.00 **SATELIT 6** **Generalni sponzor** (Boehringer Ingelheim)

19.30–21.00 *Večerja*

Sobota, 22. oktober 2022

09.00–09.30 **SATELIT 7** **Srebrni sponzor** (Eli Lilly)

09.30–11.00 **SKLOP 10** **Proste teme**

Moderatorji: **Simona Gaberšček, Mojca Jensterle Sever, Andrej Zavratnik, Primož Kotnik**

11.00–11.30 *Odmor*

11.30–12.30 **SKLOP 11** **Kako zdravimo blag presežek kortizola?**

Moderator: **Tomaž Kocjan**

- **Kirurško zdravljenje** (Antonela Sabati Rajić)
- **Konzervativno zdravljenje** (Katarina Mlekuš Kozamernik)

12.30–13.00 **SATELIT 8** **Srebrni sponzor** (AstraZeneca)

13.00–13.30 **ZAKLJUČEK KONGRESA**

13.30–14.30 *Kosilo*

Thursday, October 20th, 2022

12.00 Registration and Exhibition Opening

13.30–14.30 *Lunch*

15.00–16.00 **SESSION 1** **Reversibility of type 2 diabetes - is it real?**

Chairperson: **Draženka Pongrac Barlovič**

- **Functional beta-cell changes between development and remission of type 2 diabetes** (Andraž Stožer)
- **Weight loss and type 2 diabetes remission: lessons learned?** (Michael Lean)

16.00–17.00 **SESSION 2** **Acromegaly - The numbers or the chair?**

Chairperson: **Urša Kšela**

- **The numbers** (Tomaž Kocjan)
- **The chair** (Mojca Jensterle Sever)

17.00–17.30 **SATELLITE SYMPOSIUM 1**
Silver sponsor (Pfizer)

17.30–18.00 *Coffee break*

18.00–18.30 **CONGRESS OPENING**
Mahkota's Award

18.30–19.30 **SESSION 2** **Prospects for gene therapy**

Chairperson: **Mojca Žerjav Tanšek**

- **Genetics of short stature** (Jasna Šuput Omladič)
- **Novel treatments in achondroplasia** (Primož Kotnik)
- **Gene therapy of metabolic diseases** (Urh Grošelj)

19.30–20.00 **SATELLITE SYMPOSIUM 2**
Golden sponsor (Abbott)

20.30–21.30 *Dinner*

Friday, October 21st, 2022

08.30–09.00 **SATELLITE SYMPOSIUM 1**
Silver sponsor (Gedeon Richter)

09.00–10.00 **SESSION 4** **Functional hypogonadism: weight loss or testosterone?**

Chairperson: **Nadan Gregorič**

- **Weight loss** (Matej Rakuša)
- **Testosterone** (Kristina Groti Antonič)

10.00–10.30 **SESSION 5** **Diabetic foot screening: yesterday, today, tomorrow**

Chairperson: **Aleš Pražnikar**

- **Screening test from 1996 to 2022: messages from the database** (Vilma Urbančič Rovan)
- **Screening optimization using predictive models** (Iztok Štotl)

11.00–11.30 *Coffee break*

11.30–12.30 **SESSION 6** **80 years of radioiodine treatment**

Chairperson: **Katica Bajuk Studen**

- **Radioiodine uptake** (Katja Zaletel)
- **Radioiodine treatment** (Edvard Pirnat)
- **Radioiodine and Graves' orbitopathy** (Polona Jaki Mekjavić)
- **Radioiodine in adolescents** (Simona Gaberšček)

12.30–13.30 **SESSION 7** **Modern technologies in the treatment of diabetes**

Chairpersons: **Tadej Battelino**
Aleš Skvarča

- **Glycemic control and quality of life with closed-loop use in youth** (Nataša Bratina)
- **Modern technologies in the treatment of diabetes and physical activity** (Klemen Dovč)
- **Use of modern technologies during pregnancy** (Draženka Pongrac Barlovič)

Friday, October 21st, 2022

13.30–14.00 **SATELLITE SYMPOSIUM 4**
Golden sponsor (Novo Nordisk)

14.00–15.00 *Lunch*

15.00–16.00 **SESSION 8** **Reproductive endocrinology**

Chairperson: **Mojca Jensterle Sever**

- **The role of GLP-1 in women's reproductive health** (Vesna Šalamun)
- **The role of GLP-1 in men's reproductive health** (Nadan Gregorič)
- **Interdisciplinary management of infertility: endocrinologist and reproductive gynaecologist** (Eda Vrtačnik Bokal)

16.00–16.30 **SATELLITE SYMPOSIUM 5**
Silver sponsor (Novartis)

16.30–17.00 *Coffee break*

17.00–18.00 **SESSION 9** **Pancreatic cancer, obesity and diabetes mellitus**

Chairperson: **Andrej Janež**

- **Pancreatic cancer – data from the Cancer Registry of Republic of Slovenia** (Vesna Zadnik)
- **Pancreatic cancer: risk factors, risk assessment and screening of high-risk individuals** (Mateja Krajc)

18.00–19.00 **SATELLITE SYMPOSIUM 6**
Platinum sponsor (Boehringer Ingelheim)

19.30–21.00 *Dinner*

Saturday, October 22nd, 2022

09.00–09.30 **SATELLITE SYMPOSIUM 7**
Silver sponsor (Eli Lilly)

09.30–11.00 **SESSION 10** **Oral presentations**

Chairpersons: **Simona Gaberšček, Mojca Jensterle Sever, Andrej Zavratnik, Primož Kotnik**

11.00–11.30 *Coffee break*

11.30–12.30 **SESSION 11** **How do we treat mild autonomous cortisol excess?**

Chairperson: **Tomaž Kocjan**

- **Surgical treatment** (Antonela Sabati Rajić)
- **Conservative treatment** (Katarina Mlekuš Kozamernik)

12.30–13.00 **SATELLITE SYMPOSIUM 8**
Silver sponsor (AstraZeneca)

13.00–13.30 **CONCLUSION**

13.30–14.30 *Lunch*

PREDAVANJA
LECTURES

FUNCTIONAL CHANGES IN BETA CELLS DURING DEVELOPMENT AND REMISSION OF TYPE 2 DIABETES

Maša Skelin Klemen [1], Jan Kopecky [1], Eva Paradiž Leitgeb [1], Jasmina Kerèmar [1], Lidija Križančić Bombek [1], Viljem Pohorec [1], Ismael Valladolid-Acebes [3], Andraž Stožer [1,2,3,*], Jurij Dolenšek [1,2,*]

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Introduction

Diet-induced obesity (DIO) mouse models are a common and valuable research tool in studying pathophysiology of type 2 diabetes mellitus (T2D). Currently used animal models (e.g., high fat diet, high fat high sucrose) have some inherent methodological drawbacks, mostly due to beta cell plasticity when used from an early age, and due to the composition of the diet used to induce T2D (1–3). On the other hand, clinical studies by Taylor et al. strongly suggest that caloric restriction results in effective remission of T2D in humans (4, 5). However mechanistic explanation available at the level of beta cell function is inherently limited in human studies (6). We therefore constructed a novel mouse model of DIO that would more closely reflect T2D in humans in an attempt to decipher functional and morphological changes following caloric restriction-induced remission of

T2D. To this end, 7 days of caloric restriction (i.e., intake of 35% of the caloric intake of the control group) were employed in mice previously exposed to WD to attempt to induce DIO and then reverse the diabetic phenotype, with normalization of body mass, normalization of glucose handling and insulin sensitivity. To provide a mechanistic explanation for both the DIO and remission following caloric restriction at the level of beta cell function, we performed functional multicellular confocal calcium imaging on acute pancreas tissue slices to assess the effects of both DIO and caloric restriction on the glucose sensitivity of beta cells.

Methods

Male and female C57BL/6J were separated into three groups: western diet (WD), control diet (CD), and restricted control diet (RCD). WD and RCD mice were fed WD for 12 weeks starting from the age of 12 weeks. After 7 weeks of WD, the RCD mice received one week of restricted caloric intake (RCD, 35% caloric intake of CD) and then received CD until sacrifice. We measured weekly food and water intake, we performed intraperitoneal glucose tolerance tests (ipGTT) and insulin tolerance tests (ipITT). Calcium imaging of islets of Langerhans in acute pancreas tissue slices was performed with high temporal and spatial resolution confocal microscopy after stimulating the islets with increasing glucose concentrations (7–16 mM). To quantify their sensitivity to glucose, the frequency, duration, and active time of calcium oscillations were determined during the plateau phase of their responses.

Results

On WD, male mice developed fasting hyperglycemia, glucose intolerance, as assessed by the intraperitoneal glucose tolerance tests, and insulin resistance, as assessed by the intraperitoneal insulin tolerance tests. Notably, female mice were more resistant to the development of type 2 diabetes than males. One week of caloric restriction in the RCD group reversed fasting glycemia, glucose, and insulin tolerance to control values

and these parameters remained at control values during the following period on CD. In both control and WD mice, active time progressively increased with increasing glucose concentrations, as described previously in independent cohorts of mice of different strains (7, 8), but in WD mice, the dose-response curve was clearly left-shifted, indicating increased sensitivity of beta cells to glucose in the WD group. In other words, compensatory hyperinsulinemia observed in the WD group can be ascribed to both hyperglycemia and increased sensitivity, at least during the early stages of T2D development in our model. Similar to *in vivo* findings obtained by tolerance tests, the *in situ* changes in sensitivity obtained by calcium imaging were much less pronounced in female mice, yet still clearly detectable. After one week of caloric restriction, the dose-response curve returned to control values.

Conclusions and outlook

Our findings further elucidate the impact of caloric restriction on T2D and our animal model provides a novel platform for studying T2D. DIO induced by WD resulted in T2D with partially compensated insulin resistance, seen as fasting hyperglycemia, impaired glucose tolerance and insulin resistance. The main mechanism of beta cell adaptation during this partly compensated diabetic state was increased activity of calcium oscillations and a left shift in the dose-dependence curve. Female mice were more resistant to the WD intervention, but still showed clear signs of beta cell adaptation in the face of developing insulin resistance and glucose intolerance (9). Short-term caloric restriction completely rescued the DIO, with mice exhibiting control values of glucose tolerance, insulin sensitivity, and beta cell responsiveness to glucose, and these parameters remained at control values during maintenance on CD. Since first reports on calcium imaging in human islets indicate that the dose-response curves of beta cells in advanced T2D are right-shifted, i.e., the sensitivity of beta cells to glucose is decreased (10), in future studies, we will attempt to prolong the period of WD to track the temporal evolution of beta cell adaptation and possibly detect early dysfunction and thus the time point when caloric restriction can be expected to become less effective, which is a crucial step to make our mouse model translationally more relevant.

References

1. Irles E, Ñeco P, Lluesma M, Villar-Pazos S, Santos-Silva JC, Vettorazzi JF, et al. Enhanced glucose-induced intracellular signaling promotes insulin hypersecretion: Pancreatic beta-cell functional adaptations in a model of genetic obesity and prediabetes. Mol Cell Endocrinol. 2015;404:46-55.

2. Gonzalez A, Merino B, Marroqui L, Neco P, Alonso-Magdalena P, Caballero-Garrido E, et al. Insulin hypersecretion in islets from diet-induced hyperinsulinemic obese female mice is associated with several functional adaptations in individual beta-cells. Endocrinology. 2013;154(10):3515-24.

3. Corezola do Amaral ME, Kravets V, Dwulet JM, Farnsworth NL, Piscopio R, Schleicher WE, et al. Caloric restriction recovers impaired β-cell-β-cell gap junction coupling, calcium oscillation coordination, and insulin secretion in prediabetic mice. Am J Physiol Endocrinol Metab. 2020;319(4):E709-e20.

4. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.

5. Xin Y, Davies A, Briggs A, McCombie L, Messow CM, Grieve E, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/Counterweight-Plus weight management programme. Diabetologia. 2020;63(10):2112-22.

6. White MG, Shaw JAM, Taylor R. Type 2 Diabetes: The Pathologic Basis of Reversible β-Cell Dysfunction. Diabetes Care. 2016;39(11):2080-8.

7. Pohorec V, Križančić Bombek L, Skelin Klemen M, Dolenšek J, Stožer A. Glucose-Stimulated Calcium Dynamics in Beta Cells From Male C57BL/6J, C57BL/6N, and NMRI Mice: A Comparison of Activation, Activity, and Deactivation Properties in Tissue Slices. Front Endocrinol (Lausanne). 2022;13:867663.

8. Stožer A, Skelin Klemen M, Gosak M, Križančić Bombek L, Pohorec V, Slak Rupnik M, et al. Glucose-dependent activation, activity, and deactivation of beta cell networks in acute mouse pancreas tissue slices. Am J Physiol Endocrinol Metab. 2021;321(2):E305-e23.

9. Stožer A, Hojs R, Dolenšek J. Beta Cell Functional Adaptation and Dysfunction in Insulin Resistance and the Role of Chronic Kidney Disease. Nephron. 2019.

10. Gosak M, Yan-Do R, Lin H, MacDonald PE, Stožer A. Ca^{2+} oscillations, waves, and networks in islets from human donors with and without type 2 diabetes. Diabetes. 2022 Sep 6;db220004. doi: 10.2337/db22-0004. Online ahead of print.

WEIGHT LOSS AND TYPE 2 DIABETES REMISSION: LESSONS LEARNED?

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Until recently, teaching about type 2 diabetes (T2D) was from endocrinologists. They considered it an unexciting disease which lacked the logical mechanisms of endocrine diseases, and for which hormone replacement was not a good solution. It was regarded as inevitable disorder of ageing, mainly found in elderly people and with few complications compared to type 1 diabetes, where insulin function declines and beta-cell capacity falls, progressively and permanently, not requiring insulin treatment. Treatment was largely symptomatic and the disease and its treatment were largely ignored by many doctors and by most patients.

There have been radical changes over the past 30-40 years. T2D now affects 5-10% of western regions, 20-40% in some Asian and indigenous populations. Its disabling, painful, life-shortening complications (in increasingly young people) now dominate healthcare budgets. Large numbers of new highly expensive drugs have been developed and are prescribed to try to modify complications. The change is very clearly through populations gaining weight, at younger ages. T2D is not a primary endocrine disease: it is a nutritional disease of fat storage, and just one of many chronic disease outcomes which commonly coexist as ‘multi-morbidity’. Not everyone who

gains weight will develop T2D, but around 40% of western populations do have a genetic predisposition for metabolic syndrome, and are likely to develop T2D at some stage as they become older and more overweight.

T2D has been 'associated' with overweight and obesity for many years: the misleading word 'comorbidity' has been used. It has astronomical relative risks at high BMI, but even knowing that prediabetes progression to diabetes can be prevented by weight loss did not immediately trigger recognition that T2D is actually *caused* by weight gain with age – and thus a potentially reversible disease-process. A misunderstanding of 'obesity' (the disease-process of excess body fat accumulation) caused a failure to recognise this as the cause of T2D when body mass index is below the epidemiological cut-off of 30kg/m^2.

The DiRECT trial was designed to establish whether T2D remission could be achieved, within routine primary-care, by weight loss using an evidence-based structured diet programme (Counterweight-Plus). Intervention participants lost a mean 13.5kg with 850kcal/day for ~12weeks. New-style meals with ~50%E carbohydrate were then introduced stepwise, to maintain mean ~10kg loss at 12 months. Overall, almost half (46%) were no longer diabetic, and not requiring medication for diabetes – ie. in remission. Remission was achievable for the great majority of patients: 86% were in remission if they lost more than 15kg. Sadly, most regained weight, but with weight loss >10kg, over 70% achieved remission, at both 12 and 24 months.

About a third of participants were also able to stop their antihypertensive medications, and fatty liver disease, also common in people with T2D, was similarly resolved. With reduced prescriptions and medical consultations and admissions, health economics analysis showed that the intervention would pay for itself in 5–6 years. Patients were estimated to live longer, feel better, and cost less.

A subset of DiRECT participants underwent detailed metabolic and MRI investigations, which showed that people with T2D (despite good treatment with UK guidelines) have excess fat in liver and pancreas, and that seems to be driving T2D. With weight loss and remission, liver and pancreas fat falls to normal, the ragged sick-looking pancreas returns to a normal size and morphology, and maximal insulin production doubles, to become normal again.

DiRECT has thus confirmed that T2D is a disease of ectopic fat accumulation, within the disease-process of 'obesity'. T2D can develop at almost any BMI level, if there is already ectopic fat accumulation in vital organs. DiRECT showed that T2D is reversible for the majority of people, with weight loss soon after diagnosis, and these results have now been repeated for Arab and North African people in the DIADEM-1 trial, and in RETUNE with BMI below 27kg/m^2. Remission rate depends on weight loss. Questions remain, particularly about how to maintain weight loss after the hard work to achieve it, but remission is now a key T2D management target, and weight loss >10-15kg should be encouraged for all, as soon as possible after diagnosis, using self-help or professionally-supported diet programmes. The COVID-19 experience showed that remote and face-to-face support are equally effective for Counterweight-Plus.

Further details about the DiRECT trial, and its publications, can be found on the website: https://www.directclinicaltrial.org.uk/

ACROMEGALY – THE NUMBERS

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Introduction

Acromegaly is a rare, slowly progressive disease resulting from the increased release of growth hormone (GH) and, consequently, insulin- like growth factor I (IGF-1), which in most cases is induced by a GH-secreting pituitary tumor and rarely by ectopic secretion of GH or GH releasing hormone (GHRH). Prolonged exposure to GH excess leads to progressive somatic disfigurement and a wide range of systemic manifestations that are associated with increased mortality (1).

Numbers

GH and IGF-I assessments are the standard for assessing acromegaly disease activity at diagnosis and follow-up (2). The Endocrine Society recommends measurement of serum IGF-1 in patients with typical clinical manifestations of acromegaly, with several typical associated conditions (e. g. sleep apnea syndrome, type 2 diabetes mellitus, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension) or with a pituitary mass (3). When IGF-1 levels are elevated or equivocal, the diagnosis should

be confirmed by finding lack of suppression of GH to <0.4 µg/L following documented hyperglycemia during an oral glucose load (3, 4). Biochemical targets of an age normalized IGF-1 value and a random GH <1.0 µg/L are the suggested goals of management of acromegaly (3), as they have each been shown to correlate with mortality risk reduction (5).

An important caveat to consider is a lack of consensus for target GH and IGF-1 levels that correlate with prevention of comorbidities. IGF-1 levels correlate with comorbidities better than glucose-suppressed GH levels. IGF-1 levels may be more predictive than nadir GH for predicting insulin sensitivity and clinical symptom score after surgery (3).

A challenging clinical problem is discrepancy between GH and IGF-1 levels. Various studies have obtained different discordance rates, ranging from 5.4% to 39.5%. Their impacts over mortality and morbidity and the risk of biochemical and/or clinical recurrence are unclear (6). The proposed mechanisms to explain this phenomenon include early or partially treated disease, altered dynamics of the GH secretion after surgery, early postoperative IGF-1 assay, inappropriate cut-off point for GH suppression in the GH assays, GH nadir values not adjusted to age, sex, and body mass index, the influence of concomitant medication, inaccurate or less sensitive tests and laboratory errors, such as pre-analytical and technical pitfalls, and several co-existing physiologic and pathologic conditions. Such cases should be carefully assessed to avoid misinterpreting the activity of acromegaly or misdiagnosing a patient with acromegaly. (6, 7). Given the variability between GH and IGF-1 assays it is critical to maintain the use of the same assay in the same patient if possible throughout management (3).

Patient-related outcomes

Although treatment often results in normalization of GH and IGF-1 levels with significant clinical improvement, a proportion of patients still suffer from extensive (irreversible) late effects of acromegaly largely from musculoskeletal complications and persistent cardiovascular, endocrine, metabolic, and oncologic comorbidities (1, 8). Biochemical control does not

necessarily correlate with patient's well-being, and health-related quality of life (HRQoL) impairments might persist despite biochemical control. Therefore, treatment should not only aim to normalize biochemical outcomes but also improve patient-reported outcomes (PROs) (8). To capture the patients' perspective by measuring symptoms and HRQoL, the use of PRO measures (PROMs) in clinical trials and practice has been advocated in addition to biochemical evaluation (9–11).

A recent meta-analysis found that 34% of studies among patients with acromegaly reported discrepant results between PROs and biochemical outcomes. The percentage of discrepant results was slightly higher among studies measuring HRQoL (38%) compared to studies measuring symptoms (32%). More than half (56%) of the discrepant studies reported an improvement in biochemical outcomes, without improvement in PROs. No clear determinants of these discrepancies were identified. Studies that included participants who had been treated previously showed a tendency toward higher odds of discrepancy compared to studies in treatment-naïve patients. The authors speculated, the discrepancies may result from the fact that PROMs and biochemical parameters measure different aspects of health and are therefore complementary. Every patient might have an individual optimal hormonal setpoint, making it difficult to rely on biochemical parameters alone. Furthermore, some symptoms and reduced HRQoL may be caused by irreversible damage that is unresponsive to treatment. Therefore, both PROMs and biochemical outcome parameters are needed to obtain a comprehensive view of disease activity (12).

Conclusion

A patient-centered approach, accounting for biochemical parameters, comorbidities, treatment complications, and HRQoL measures, should all be considered in treatment decisions (8). Scoring systems such as SAGIT (Signs and symptoms, Associated comorbidities, Growth hormone levels, IGF-1 levels, and Tumor profile) (9) and ACRODAT (10) are useful to assess overall disease activity while general and acromegaly-specific HRQoL instruments such as AcroQoL (11) can be helpful in identifying specific factors for follow-up (8).

References

1. Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, et al. Acromegaly. Nat Rev Dis Primer. 2019;5(1):1–17.
2. Fleseriu M, Biller BMK, Freda PU, Gadelha MR, Giustina A, Katznelson L, et al. A Pituitary Society update to acromegaly management guidelines. Pituitary. 2021;24(1):1–13.
3. Katznelson L, Laws ER, Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(11):3933–51.
4. Melmed S, Bronstein MD, Chanson P, Klibanski A, Casanueva FF, Wass JAH, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552–61.
5. Holdaway IM, Bolland MJ, Gamble GD. A meta-analysis of the effect of lowering serum levels of GH and IGF-I on mortality in acromegaly. Eur J Endocrinol. 2008;159(2):89–95.
6. Zeinalizadeh M, Habibi Z, Fernandez-Miranda JC, Gardner PA, Hodak SP, Challinor SM. Discordance between growth hormone and insulin-like growth factor-1 after pituitary surgery for acromegaly: a stepwise approach and management. Pituitary. 2015;18(1):48–59.
7. Peixe C, Sánchez-García M, Grossman AB, Korbonits M, Marques P. Biochemical discrepancies in the evaluation of the somatotroph axis: Elevated GH or IGF-1 levels do not always diagnose acromegaly. Growth Horm IGF Res. 2022;64:101467.
8. Giustina A, Barkan A, Beckers A, Biermasz N, Biller BMK, Boguszewski C, et al. A Consensus on the Diagnosis and Treatment of Acromegaly Comorbidities: An Update. J Clin Endocrinol Metab. 2020;105(4):dgz096.
9. Giustina A, Bevan JS, Bronstein MD, Casanueva FF, Chanson P, Petersenn S, et al. SAGIT®: clinician-reported outcome instrument for managing acromegaly in clinical practice--development and results from a pilot study. Pituitary. 2016;19(1):39–49.
10. van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, et al. Development of ACRODAT®, a new software medical device to assess disease activity in patients with acromegaly. Pituitary. 2017;20(6):692–701.
11. Webb SM, Badia X, Surinach NL, Spanish AcroQol Study Group. Validity and clinical applicability of the acromegaly quality of life questionnaire, AcroQoL: a 6-month prospective study. Eur J Endocrinol. 2006;155(2):269–77.
12. van der Meulen M, Zamanipoor Najafabadi AH, Broersen LHA, Schoones JW, Pereira AM, van Furth WR, et al. State of the Art of Patient-reported Outcomes in Acromegaly or GH Deficiency: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab. 2022;107(5):1225–38.

ACROMEGALY: THE NUMBERS OR THE CHAIR?

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Biochemical control of acromegaly is associated with reduced morbidity and mortality and is recognized as the most important for the long-term prognosis of acromegaly. The numbers are therefore the main-core of the disease management. Fortunately, nowadays, a multimodal therapeutic approach allows the achievement of biochemical control in the vast majority of patients with acromegaly (1, 2).

Based on the biochemical control, the patients are classified as either cured after surgery, controlled on pharmacotherapy, or uncontrolled. They are considered cured after transsphenoidal surgery if nadir GH level during an OGTT is <0.4 µg/L and age- and gender-adjusted IGF-1 levels normalized. When they are not cured by surgery, they are classified controlled on pharmacotherapy, if age- and gender-adjusted IGF-1 levels are up to 1-2-1.3 times the upper level of normal (3). Recently, GH and mean GH profile have also been considered as an important number to control in patients that are on pharmacotherapy. In the future, some limitations of biochemical assessment still need to be overcome by improving the methodology to assess IGF-1 and GH, in particularly for those on pegvisomant, and by better interpretation of several potential impacts on the biochemical control.

However, biochemical profiles and clinical features may give discordant information. Some clinical features do not relief after biochemical normalization. Patients that are biochemical well-controlled might report as poor disease related quality of life (QoL) than those with biochemically uncontrolled disease. This well-documented discordance between patient- and clinician-perception of the disease control could be reduced by using specific clinician- and patient-reported outcome tools (4, 5).

The clinician-reported outcome tools such as SAGIT Instrument (SAGIT) and ACRODAT provide objective measurement of present signs and symptoms, comorbidities, tumour profile, and biochemical parameters (6, 7). On the other hand, the Patient-assessed Acromegaly Symptom Questionnaire (PASQ), Acromegaly Quality of Life Questionnaire (AcroQoL), the Acromegaly Treatment Satisfaction Questionnaire (AcroTSQ), the enlargement of the extremities questionnaire, and the acromegaly comorbidities and complaints questionnaire allow patients to give their perspectives on symptoms and QoL (8, 9). Although these tools were designed to assist clinicians in acromegaly staging, treatment outcome assessment, and adapting patient management in a standardized way, they are still not commonly conducted in everyday clinical practice (7, 9).

We emphasise the complementary nature of »Clinician- and Patient-Reported Outcome« tools in the management of acromegaly. The correlations between these specific tools could help us to identify some modifiable parameters that should be further addressed beyond biochemical control to assure an updated patient-centred personalized approach in a standardized way (10). In summary, the strategies to improve disease control from both, clinicians' and patients' perspective, should include treatment of the disease, treatment of comorbidities and addressing individual needs of the patient.

References

1. Manjila S, Wu OC, Khan FR, Khan MM, Arafah BM, Selman WR. Pharmacological management of acromegaly: a current perspective. Neurosurg Focus. 2010;29(4):E14.
2. Rowles SV, Prieto L, Badia X, Shalet SM, Webb SM, Trainer PJ. Quality of life (QOL) in patients with acromegaly is severely impaired: use of a novel measure of QOL: acromegaly quality of life questionnaire. J Clin Endocrinol Metab. 2005;90(6):3337-41.
3. Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, et al. Multidisciplinary management of acromegaly: A consensus. Rev Endocr Metab Disord. 2020;21(4):667-678.
4. Gurel MH, Bruening PR, Rhodes C, Lomax KG. Patient perspectives on the impact of acromegaly: results from individual and group interviews. Patient Prefer Adherence. 2014;8:53-62.
5. Geer EB, Sisco J, Adelman DT, Ludlam WH, Haviv A, Gelbaum D, et al. Observed discordance between outcomes reported by acromegaly patients and their treating endocrinology medical provider. Pituitary. 2020;23(2):140-148.
6. van der Lely AJ, Gomez R, Pleil A, Badia X, Brue T, Buchfelder M, et al. Development of ACRODAT®, a new software medical device to assess disease activity in patients with acromegaly. Pituitary. 2017;20(6):692-701.
7. Giustina A, Bevan JS, Bronstein MD, Casanueva FF, Chanson P, Petersenn S, et al. SAGIT®: clinician-reported outcome instrument for managing acromegaly in clinical practice--development and results from a pilot study. Pituitary. 2016;19(1):39-49.
8. an der Meulen M, Zamanipoor Najafabadi AH, Broersen LHA, Schoones JW, Pereira AM, van Furth WR, et al. State of the Art of Patient-reported Outcomes in Acromegaly or GH Deficiency: A Systematic Review and Meta-analysis. J Clin Endocrinol Metab. 2022;107(5):1225-38.
9. Giustina A, Bronstein MD, Chanson P, Petersenn S, Casanueva FF, Sert C, et al. International Multicenter Validation Study of the SAGIT® Instrument in Acromegaly. J Clin Endocrinol Metab. 2021;106(12):3555-68.
10. Herman R, Goričar K, Janež A, Jensterle M. Clinical Applicability of Patient- and Clinician-Reported Outcome Tools in the Management of Patients With Acromegaly. Endocr Pract. 2022; 28(7):678-683.

GENETICS OF SHORT STATURE

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Linear growth in humans is regulated by different factors from the embryonic stage to childhood, adolescence until final height. During fetal stage insulin and growth factors have prevalent influence on growth. Later, in the early childhood growth hormone-insulin like growth factor 1 (GH-IGF-1) axis becomes the main driver of linear growth. During puberty, sex hormones have an important role in the increased growth velocity and are at the same time responsible for the closure of the growth plate, indicating the end of linear growth. Recently the role of non-GH-IGH-1 hormonal factors in linear growth was also determined. Local factors in the growth plate were determined to be important not only in skeletal dysplasia but also in children with so called idiopathic short stature (ISS) (1, 2).

Height is a polygenetic trait, and although the environment has an important role in linear growth, it is estimated that genetics explains up to 60% of height variability. There are several hundred loci associated with human height having been identified by genome-wide association studies, and an increasing number of novel monogenic causes of short stature have recently been proposed. Determining the genetic cause of short stature

is not important only from the diagnostic point-of-view, but also could influence the therapeutic decisions at the start of treatment with human recombinant GH (hr-GH) and long-term management (1, 2).

GH-IGF-1 axis defects

Growth can be affected at various levels of the GH-IGF-1 axis. GH deficiency is a major cause of growth failure. Genetic caused associated with GH deficiency are pathogenic variants in genes for growth hormone (*GH1*) or the GH-releasing hormone receptor (*GHRHR*). In addition, several genes associated with the development of pituitary are also associated with GH deficiency (and possibly deficiencies of other pituitary hormones), namely *POU1F1, PROP1, LHX3, LHX4, HESX1*. Monogenic causes can be determined in up to 10% of subjects diagnosed with GH deficiency, the percentage being even higher if multiple pituitary hormone deficiency was determined. Determining the genetic cause of GH deficiency is important for clinical outcomes and GH treatment. E.g. those with identified pathogenic variants in the genes associated with GH deficiency tended to be shorter at recombinant GH therapy start, however had a better treatment response (3).

GH deficiency usually doesn't affect intrauterine growth. On the other hand, resistance to GH is associated with impaired intrauterine growth, newborn being born small for gestational age. Resistance to GH is associated with pathogenic variants in the GH receptor (*GHR*) – so called Laron syndrome. Distally from GHR, pathogenic variants in the *STAT5B* gene are associated with short stature, low IGF-1 levels, normal GH levels and additional clinical problems as are severe immune deficiency and pulmonary problems. *PAPP-A2* is a newly determined cause of progressive post-natal growth. Pathogenic variants in the *IGF1* and *IGF2* genes are a further cause of short stature. Homozygous states are associated with severe short stature and additional clinical signs, whereas heterozygous states are also determined in ISS. Imprinting defects in the *IGF2* gene are associated with Silver-Russell syndrome and Temple syndrome. Further down the GH-IGF-1 axis are defects in the *IGF1R* gene, that are featured by resistance to IGF-1. The clinical signs are usually more complex than isolated short stature, microcephaly

and psychomotor retardation being the most frequent additional signs. Children with GH resistance benefit from human recombinant IGF-1 therapy either as monotherapy or in combination with hr-GH (4).

Non-GH-IGF-1 axis defects

Until recently most of the genetic diagnostic process has focused on the GH-IGF-1 axis. It was however determined that surprisingly large number of ISS cases with or without extremities disproportions can be attributed to non-GH-IGF-1 axis genes (2).

Pathogenic variants in the *FGFR3* gene are associated with skeletal dysplasia's achondroplasia and hypochondroplasia in an autosomal dominant manner, linked to specific genetic variants. In addition, several heterozygous variants in this gene were also associated with ISS. Results regarding rh-GH treatment of children with *FGFR3* mutations are controversial (6).

ACAN gene encodes a proteoglycan, that is a key component in the cartilage extracellular matrix of the growth plate. Abnormalities in the *ACAN* gene are associated with proportionate or mildly disproportionate short stature and premature closure of the growth plates. Therapy with hr-GH is reported to be effective (7).

One of the genes that is frequently associated with short stature is SHOX, located to the X chromosome. Phenotypically there is a wide variation from skeletal dysplasia of Leri-Weill to short stature without other features. Product of the *SHOX* gene is a transcription factor that regulated several genes that have important role in the growth plate as are *ACAN* and *FGFR3.* Treatment of children with pathological variants in the *SHOX* gene with hr-GH was determined to be efficient (8).

NPR2 gene is another gene expressed in the growth plate and associated with ISS. Homozygous mutations in *NPR2* gene are associated with a severe acromesomelic dysplasia type Maroteaux. Heterozygous mutations are linked to ISS. Treatment with hr-GH has been determined as efficient in several studies (9).

Conclusions

Following the development of molecular-genetic techniques, it is possible to perform more in-depth genetic analysis, more quickly, and more affordably. By determining the genetic cause of short stature, the management can be targeted, tailored to the individual and safer. It seems that genetic analysis might soon be a standard procedure in the diagnosis of short stature due to ever wider spectrum of clinical features linked with short stature.

References

1. Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, et al. Consensus statement on the diagnosis and treatment of children with idiopathic short stature: A summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. J Clin Endocrinol Metab. 2008;93(11):4210–7.
2. Argente J, Tatton-Brown K, Lehwalder D, Pfäffle R. Genetics of Growth Disorders-Which Patients Require Genetic Testing? Front Endocrinol (Lausanne). 2019;10:602(1–15).
3. Wit JM, Oostdijk W, Losekoot M, van Duyvenvoorde HA, Ruivenkamp CA, Kant SG. MECHANISMS IN ENDOCRINOLOGY: Novel genetic causes of short stature. Eur J Endocrinol. 2016;174(4):R145–73.
4. Walenkamp MJ, Losekoot M, Wit JM. Molecular IGF-1 and IGF-1 receptor defects: from genetics to clinical management. Endocr Dev. 2013;24:128–37.
5. Walenkamp MJE, Robers JML, Wit JM, Zandwijken GRJ, van Duyvenvoorde HA, Oostdijk W, Hokken-Koelega ACS, Kant SG, Losekoot M. Phenotypic Features and Response to GH Treatment of Patients With a Molecular Defect of the IGF-1 Receptor. J Clin Endocrinol Metab. 2019;104(8):3157–71.
6. Mamada M, Yorifuji T, Kurokawa K, Kawai M, Momoi T, Nakahata T. Prevalence of Mutations in the FGFR3 Gene in Individuals with Idiopathic Short Stature. Clin Pediatr Endocrinol. 2006;15(2):61–4.
7. Stavber L, Hovnik T, Kotnik P, Lovrečić L, Kovač J, Tesovnik T, et al. High frequency of pathogenic ACAN variants including an intragenic deletion in selected individuals with short stature. Eur J Endocrinol. 2020;182(3):243–53.
8. Faienza MF, Chiarito M, Brunetti G, D'Amato G. Growth plate gene involment and isolated short stature. Endocrine. 2021;71(1):28–34.
9. Stavber L, Gaia MJ, Hovnik T, Jenko Bizjan B, Debeljak M, Kovač J, et al. Heterozygous NPR2 Variants in Idiopathic Short Stature. Genes (Basel). 2022;13(6):1065.

NOVEL TREATMENT OPTIONS IN ACHONDROPLASIA

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Achondroplasia (ACH) is the most common form of skeletal dysplasia. Incidence is estimated to be 1:25.000–30.000. It is characterized by disproportionate rhizomelic short stature, hypoplasia of the midface, and macrocephaly. Numerous orthopedic and neurological complications are associated with the disease (1).

ACH is caused by a gain-of-function mutation in the fibroblast growth factor-3 receptor (FGFR3) gene, a member of the tyrosine kinase receptor family (2). ACH is inherited in an autosomal dominant manner and is characterized by full penetration. Excessive FGFR3 activation results in inhibition of cartilage tissue formation at the level of chondrocyte proliferation, hypertrophy, differentiation, and synthesis of the extracellular matrix (3).

Therapy options for achondroplasia are limited. Active follow-up and symptomatic treatment of the complications present the forefront of patient management. Growth hormone supplementation has not shown promising results and is not viewed as a standard treatment for achondroplasia. The progress in the understanding of ACH pathogenesis has led to the development of several therapeutic strategies for

modulating excessive FGFR3 activation. Approaches are varied and include inhibiting the tyrosine kinase activity of FGFR3 (infigratinib), producing artificial FGFR3 as a decoy for FGF ligand (recifercept), inhibition of FGFR3 downstream signaling pathways (meclizine, C-type natriuretic peptide analogs (CNP)), modulation of growth via NPR2 receptor (CNP analogs) and use of aptamers or monoclonal antibodies to prevent binding of FGF to its receptor (aptamer RBM-007, vofamatab). The investigations into analogs of CNP, especially vosorotide, are currently the most advanced (4).

Vosoritide

Vosoritide is a recombinant CNP analog. Preclinical studies in healthy mice and cynomolgus monkeys have shown the efficacy of daily subcutaneous vosoritide applications on endochondral bone growth stimulation without causing significant changes in bone quality parameters (5). In 2021, results of the extension phase 3 clinical trial in children with ACH aged between 5 to 18, receiving vosoritide 15 µg/kg once daily in subcutaneous injection, were published. An increase in annualized growth velocity was observed, with 3.52 cm of height gain over a 2-year treatment period in comparison to untreated patients. In addition, improvement in the proportionality of body segments and no acceleration of the bone maturation process was observed (6). Mild adverse effects such as reactions at the injection site occurred in up to 73% of patients, and in 23% mild, transient, in majority asymptomatic hypotension was observed after vosoritide application (7). Vosoritide was approved by both EMA and FDA for the treatment of ACH in children from the age of 2 years until their growth plates are closed (8, 9). Vosoritide's effect on final adult height and prevention of neurological and orthopedic complications requiring surgical interventions is yet to be established. Current ongoing trials investigating its safety and efficacy in infants, young children, and those at risk of requiring cervical-medullary decompression surgery, will provide further insights into treatment effects on growth, proportionality, and other medical complications of ACH (10). In addition, long-acting CNP analogs, that would allow once weekly or once monthly applications, with equal or possibly increased efficiency are in the process of development (11).

TransCon CNP

TransCon CNP is another therapeutic option that might soon be available for the treatment of children with AP. In TransCon CNP, CNP is conjugated via a cleavable linker to a polyethylene glycol carrier molecule, that prolongs CNP's half-life, as a consequence of increased resistance to the action of neutral endopeptidase and minimizing renal clearance. The cleavage process results in slow, sustained CNP release, leading to continuous exposure of CNP at the growth plate. Its long half-life also allows convenient weekly subcutaneous administrations (12).

Preclinical data in healthy cynomolgus monkeys showed that treatment with TransCon CNP subcutaneously once per week resulted in significant growth increases in body, tail, and long bones compared to controls. An increase in height was also more pronounced in comparison to the animals receiving a daily dose of CNP analog with the same amino acid sequence as vosorotide (5% vs 3%, respectively), and no significant changes in bone quality were observed with both treatments. Moreover, sustained CNP release resulted in lower systemic CNP peak levels and has not been associated with adverse cardiovascular effects in monkeys treated with repeated weekly doses up to 100 µg/kg (12). The safe cardiovascular profile has also been recently confirmed in the first human clinical trial in healthy adult males receiving single doses of TransCon CNP up to 150 µg/kg (13). Phase 2 of the TransCon CNP clinical trial to assess its safety, tolerability, and effect on annual growth velocity started in June 2020 is still ongoing. TransCon CNP will be administered subcutaneously once per week for 52 weeks in children with achondroplasia aged 2–10 years (study identifier NCT04085523).

References

1. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007;370(9582): 162–72.
2. Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet J-M, Maroteaux P, et al. Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature. 1994;371(6494):252–4.
3. Kim J-M, Yang Y-S, Park KH, Oh H, Greenblatt MB, Shim J-H. The ERK MAPK pathway is essential for skeletal development and homeostasis. Int J Mol Sci. 2019;20(8):1803.
4. Wrobel W, Pach E, Ben-Skowronek I. Advantages and disadvantages of different treatment methods in achondroplasia: A review. Int J Mol Sci. 2021;22(11):5573.
5. Wendt DJ, Dvorak-Ewell M, Bullens S, Lorget F, Bell SM, Peng J, et al. Neutral Endopeptidase-Resistant C-Type Natriuretic Peptide Variant Represents a New Therapeutic Approach for Treatment of Fibroblast Growth Factor Receptor 3–Related Dwarfism. J Pharmacol Exp Ther. 2015;353(1):132–49.
6. Savarirayan R, Tofts L, Irving M, Wilcox WR, Bacino CA, Hoover-Fong J, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet Med. 2021;23(12):2443-2447.
7. Savarirayan R, Tofts L, Irving M, Wilcox W, Bacino CA, Hoover-Fong J, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: A randomised, double-blind, phase 3, placebo-controlled, multicentre trial. Lancet. 2020;396(10252):684–92.
8. European Medicines Agency [Internet]. Vosoritide: Summary of Product Characteristics [cited 2021 Oct 22]. Available from: https://www.ema.europa.eu/en/documents/product-information/voxzogo-epar-product-information_en.pdf.
9. U.S. Food And Drug Association [Internet]. FDA Approves First Drug to Improve Growth in Children with Most Common Form of Dwarfism [cited 2021 Oct 19]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-improve-growth-children-most-common-form-dwarfism.
10. Savarirayan R, Irving M, Maixner W, Thompson D, Offiah AC, Connolly DJA, et al. Rationale, design, and methods of a randomized, controlled, open-label clinical trial with open-label extension to investigate the safety of vosoritide in infants, and young children with achondroplasia at risk of requiring cervicomedullary decompression surgery. Sci Prog. 2021;104(1):368504211003782.
11. S chneider EL, Carreras CW, Reid R, Ashley GW, Santi DV. A long-acting C-natriuretic peptide for achondroplasia. Proc Natl Acad Sci USA. 2022;119(30):e2201067119.
12. Breinholt VM, Rasmussen CE, Mygind PH, Kjelgaard-Hansen M, Faltinger F, Bernhard A, et al. TransCon CNP, a sustained-release C-type natriuretic peptide prodrug, a potentially safe and efficacious new therapeutic modality for the treatment of comorbidities associated with fibroblast growth factor receptor 3–related skeletal dysplasias. J Pharmacol Exp Ther. 2019;370(3):459–71.
13. Bharucha K, Ota S, Christoffersen ED, Mygind P, Viuff D, Leff J. TransCon CNP: Potential for a once weekly novel therapy in children with achondroplasia. In: Bone Abstracts. Abstract Book: 9th International Conference on Children's Bone Health. 2019 Jun 22-25, Salzburg, Austria.

GENE THERAPY FOR METABOLIC DISORDERS

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Introduction

In the last few years, we have witnessed the first major series of clinically useful therapies for certain genetic disorders or for cancer, which are already significantly changing the lives of still very few patients, also in our country (1, 2). At the same time, many research studies in this field are being conducted in various stages of research, with many more new therapies can be expected in the relatively near future. Since 2018, when the first Slovenian patient with inborn error of metabolism (IEM) was referred abroad for experimental gene therapy, several other patients with various rare congenital diseases have been genetically treated at our institution (1, 2). In December 2021, the first successful application of gene therapy in Slovenia was carried out at the University Children's Hospital, UMC Ljubljana, in a child with spinal muscular atrophy, which represents a new important milestone for our area. It is also worth mentioning the very rapid progress that we are witnessing at the same time in the field of treating certain rare types of blood cancers with genetic therapy (i.e. treatment with CAR-T lymphocytes); in 2019, the first Slovenian pediatric patient was already treated abroad in this way, and it is planned for this

type of therapies to be produced and administered in our country in a near future.

Twelve different gene therapies are currently approved by the European Medicines Agency (EMA). These include therapies for rare forms of blindness and leukemia, spinal muscular atrophy, and a type of congenital immunodeficiency. This may be negligible compared to around 8,000 known rare diseases, most of which are genetically determined, but it is expected that the number of approved gene therapies will gradually but steadily increase in the coming years (1, 2).

In 2012, the first gene therapy approved in Europe was the therapy for recurrent lipoprotein lipase deficiency pancreatitis (Glybera, uniQure), an extremely rare IEM that causes extremely elevated triglyceride levels. This therapy was later withdrawn (in 2017) due to a lack of commercial interest (due to very few candidates for therapy and also due to a very high price demanded). Nevertheless, the arrival of this drug on the market stimulated the development of other gene therapies (1,2).

Our experiences with gene therapies for metabolic disorders

Between 2018 and 2021, we referred four of our patients abroad for experimental gene therapy, one with MPS I, two with MPS IIIa, and one with metachromatic leukodystrophy (in collaboration with pediatric neurologists), who were later successfully treated and continue to be regularly monitored at our institution, in cooperation with both study centers. The details of the treatment of two of these patients are briefly summarized as follows (1, 2).

Patient with MPS I: Development in the first year was as expected, then regression in speech development and unsteady gait were noticed. At the age of 18 months, he was examined by developmental pediatrician, where hypertelorism, a wide nasal root, a bulging forehead, and sharp facial features were noted. Later, hepatomegaly, flexion contractures in the knee, and umbilical hernia were also found. He was referred to our department, where soon after, MPS I was confirmed. Just before the age of two, an ex

vivo application of gene therapy was performed with the transplantation of hematopoietic stem cells treated with a lentiviral vector (Ospedale San Raffaele, Milan, Italy; sponsored by IRCCS San Raphael). The patient is regularly monitored by the study center in Italy and in parallel also at our department, where we currently note a favorable course of the disease, but the final outcome is not yet clear.

Patient with MPS IIIA: The diagnosis was made pre-symptomatically, in the neonatal period, because his older sibling (in whom unfortunately, the disease was already advanced at that time) had the same diagnosis a short time before. Neonatally, only a coarser facial features were described, but otherwise there were no other deviations. The presence of known familial genetic alterations of the SHGS gene was confirmed. At the age of 6 months, inclusion in a gene therapy clinical trial in Spain was planned, but unfortunately, due to the COVID-19 epidemic, the treatment was not carried out until the age of 9 months. A single application of in vivo gene therapy with the AAV9 vector was then performed (Hospital Universitario Santiago de Compostela, Santiago de Compostela, Spain; sponsored by Aboena Therapeutics). The patient is regularly monitored by the study center in Spain and, in parallel, at our department, which is included in the research protocol as an associated study center. For now, we are observing a very favorable course of the disease, but the final outcome is not yet clear.

Conclusions

Gene therapy represents an important turning point for patients with many hitherto incurable congenital genetic diseases, but is still available for few diseases only. The last decade has brought a great progress in this field, including in Slovenia; gene therapy was successfully used in several Slovenian patients in the last few years. It is expected that in the next decade progress in this area will be even more significant, which we must take into account when planning and organizing activities in this area. Importanly, an early (i.e. in newborns) detection of the diseases that will become “genetically curable “ will become an imperative. We need to

continue following the most developed countries, so that we can introduce innovations into practice as quickly as possible.

Nevertheless, there remain many ethical challenges and open questions regarding gene therapy. Among these, it is worth mentioning in particular: the very high price of available therapies (which on the other hand, is in most cases lower than the long-term treatment of the same patients with other therapies, such as e.g. enzyme replacement therapy or factor therapy in hemophilia); the problem of sufficient production and, especially in the case of the ex vivo approach, also of the distribution of gene therapy; inability to treat diseases caused by changes in several genes or changes at the level of chromosomes; the long-term safety of gene therapy is also not entirely clear due to short follow up periods; the problem of treating patients who previously have antibodies against the viral vector. Above all, it will probably be possible to treat only few patients for a long time. Consequently, for a while, gene therapy will not yet transform the treatment of the entire group of patients with rare diseases.

References

1. Lah B, Jalšovec T, Drole Torkar A, Kodrič J, Battelino S, Žerjav Tanšek M, et al. Gensko zdravljenje pri mukopolisaharidozi tipa IIIa: predstavitev primerov. Slov Pediatr 2022; 29(2): 10–15.

2. Jalšovec T, Lah B, Drole Torkar A, Kodrič J, Žerjav Tanšek M, Avčin SL, et al. Gensko zdravljenje otroka z mukopolisaharidozo tipa I - prikaz primera prvega uspešnega genskega zdravljenja slovenskega pacienta v tujini. Zdrav vestn. In press 2022.

FUNCTIONAL HYPOGONADISM: WEIGHT LOSS OR TESTOSTERONE? WEIGHT LOSS

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Functional hypogonadism (FH) usually presents a more subtle clinical picture, with non-specific symptoms and usually no overt signs of androgen deficiency. However, it can present with clinical symptoms or signs similar to classical hypogonadism (1). Although sexual symptoms as decreased frequency of morning erection, decreased frequency of sexual thoughts and erectile dysfunction were more frequently associated with low testosterone (T) in community dwelling middle aged and elderly European males. For the diagnosis of FH, the presence of symptoms and total T <8 nmol/L or total T <11 nmol/L and calculated free T <220 pmol/L should be established (2).

The overall prevalence of FH is estimated to 2.1–4.8%, and increases with age (2, 3). Obesity of all grades, especially World Health Organisation class III obesity (BMI>40 kg/m2), is a major and increasingly common cause of low T (1). In meta-analysis of 68 studies and almost 20.000 men with obesity, 42.8% had serum total T <10.4 nmol/L (4). Based on mendelian randomisation analysis on 7446 participants, an increase of BMI from 25 kg/m^2 to 30 kg/m^2 is associated with a decrease in serum testosterone concentration of 13–15% (5).

European Academy of Andrology guidelines on investigation, treatment and monitoring of functional hypogonadism in men recommends lifestyle changes, including physical exercise and weight reduction, in overweight and obese men with functional hypogonadism, since weight loss may increase T concentration (1). Longitudinal results of European Male Ageing Study show that total T increased in men who lost at least 5% weight during mean follow-up of 4.4±0.3 years. T increment was higher with more weight loss, the highest when >15% of weight, with recovery from secondary hypogonadism (6).

Meta-analysis of 22 trials assessed the effect of low-calorie diet on hypogonadism. Meta-analysis included 567 patients of average 44.9 years and mean BMI of 36.0 kg/m^2, and a mean follow up of 23 weeks. Trials differed in basal total T and types of diets. Low calorie diets result in significant increase in total T, SHBG and free T. Meta-regression analysis showed that higher weight reduction is associated with a higher T increase, meaning that each 5 kg of weight reduction results in 1 mmol/L increase (7).

Meta-analysis of male patients who underwent bariatric surgery (BS) and reduced BMI from 46.60±6.42 kg/m^2 to 30.14±4.6 kg/m^2 in 12 months showed a rise in total T (MD 7.32; 95% CI 5.44 to 9.20; P < 0.00001) and free T (SMD 0.99; 95% CI 0.54 to 1.44; P < 0.0001). Also, LH, FSH and SHBG increased significantly (8). When morbidly obese patients with hypogonadism were compared with non-hypogonadal patients, total and free T significantly increased only in hypogonadal patients post BS (9). In obese adolescent men with subnormal T, reduction of body weight for one-third, which was maximal at 24 months post-surgery, resulted in increased total and calculated free T up to 5 years (10). In addition to hormone profile also erectile function and symptoms of hypogonadism improved (11).

Antihyperglycemic drug liraglutide is a glucagon like peptide-1 analogue. It also induces weight loss. In a 16-week randomised clinical trial 3.0 mg/d liraglutide was compared to 1% T gel. Liraglutide reduced weight by 6%. Both treatments ameliorated sexual symptoms and significantly increased total T, although the increase was more evident with T gel (5.9 vs. 2.6 mmol/L). Liraglutide marginally improved LH (0.7 mU/L), in comparison to T gel which reduced it (12).

Weight reduction should be the first line of management and strongly encouraged in all overweight and obese men with low T. Significant collateral health benefits may also accrue from these life style changes, potentially offering valuable opportunities for preventative care in middle-aged men.

References

1. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males. Endorsing organization: European Society of Endocrinology. Andrology. 2020;8(5):970-87.
2. Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, et al. EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010;363(2):123-35.
3. Rastrelli G, Corona G, Tarocchi M, Mannucci E, Maggi M. How to define hypogonadism? Results from a population of men consulting for sexual dysfunction. J Endocrinol Invest. 2016;39(4):473-84.
4. van Hulsteijn LT, Pasquali R, Casanueva F, Haluzik M, Ledoux S, Monteiro MP, Salvador J, Santini F, Toplak H, Dekkers OM. Prevalence of endocrine disorders in obese patients: systematic review and meta-analysis. Eur J Endocrinol. 2020;182(1):11-21.
5. Eriksson J, Haring R, Grarup N, Vandenput L, Wallaschofski H, Lorentzen E, et al. Causal relationship between obesity and serum testosterone status in men: A bi-directional mendelian randomization analysis. PLoS One. 2017;12(4):e0176277.
6. Camacho EM, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, et al. EMAS Group. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. Eur J Endocrinol. 2013;168(3):445-55.

7. Corona G, Rastrelli G, Morelli A, Sarchielli E, Cipriani S, Vignozzi L, et al. Treatment of Functional Hypogonadism Besides Pharmacological Substitution. World J Mens Health. 2020;38(3):256-70.

8. Al Qurashi AA, Qadri SH, Lund S, Ansari US, Arif A, Durdana AR, et al. The effects of bariatric surgery on male and female fertility: A systematic review and meta-analysis. Ann Med Surg (Lond). 2022;80:103881.

9. Samavat J, Facchiano E, Lucchese M, Forti G, Mannucci E, Maggi M, et al. Hypogonadism as an additional indication for bariatric surgery in male morbid obesity? Eur J Endocrinol. 2014;171(5):555-60.

10. Dhindsa S, Ghanim H, Jenkins T, Inge TH, Harmon CM, Ghoshal A, et al. High prevalence of subnormal testosterone in obese adolescent males: reversal with bariatric surgery. Eur J Endocrinol. 2022;186(3):319-327.

10. Machado FP, Rhoden EL, Pioner SR, Halmenschlager G, de Souza LVB, Lisot BC, et al. Weight Loss Through Bariatric Surgery in Men Presents Beneficial Effects on Sexual Function, Symptoms of Testosterone Deficiency, and Hormonal Profile. Sex Med. 2021;9(4):100400.

12. Jensterle M, Podbregar A, Goričar K, Gregorič N, Janež A. Effects of liraglutide on obesity-associated functional hypogonadism in men. Endocr Connect. 2019;8(3):195-202.

FUNCTIONAL HYPOGONADISM – TREATMENT WITH TESTOSTERONE THERAPY

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Hypogonadism in males is classified as either organic, due to medical disease of the hypothalamic-pituitary-testicular axis (HPT), or as functional (1). Functional hypogonadism (FH) is defined as the coexistence of androgen deficiency clinical features and lowered serum testosterone concentrations occurring in the absence of both intrinsic structural HPT axis pathology (e.g. Klinefelter's syndrome, pituitary tumor) and specific pathologic conditions suppressing the HPT axis (*e.g.* Cushing's syndrome, prolactinoma) in middle-aged or older men (2).

Diagnosis of FH should only be confirmed after the exclusion of organic causes of hypogonadism (3). In contrast to organic hypogonadism, FH may be potentially reversible if underlying causes are identified and adequately treated or removed, whereas organic hypogonadism is generally irreversible (1,2). The vast majority of FH occurrences are associated with aging and comorbidities such as obesity, type 2 diabetes (T2D), or metabolic syndrome (MetS) (4). The community prevalence estimates of FH in middle-aged and older men vary from 2.1% to 12.3% (1). Approximately 50% of males with T2D, aged >40 years, exhibit decreased total testosterone levels (5). As much

as 45.0-57.5% of male FH prevalence is attributable to obesity and related causes (6).

Diagnostic criteria for FH include the simultaneous presence of low serum testosterone (total testosterone <11 nmol/L and free testosterone <220 pmol/L) and three sexual symptoms (erectile dysfunction, reduced frequency of sexual thoughts, and morning erections) (3, 7).

Treatment options in middle-aged and older males with FH

Obesity-related FH aims to achieve significant weight loss through dietary modifications such as caloric restriction, increased physical activity, or by means of bariatric surgery (3, 8). Few randomized clinical studies have evaluated the impact of diet and physical activity on testosterone levels in obese men with FH, with conflicting results. Some of them showed an increase in testosterone (9), others showed no change (10), and one small study has shown a decrease in testosterone levels (11). Longitudinal data from the European Male Aging Study (EMAS) showed that weight loss can increase testosterone levels in obese men, and the rise in testosterone level is proportional to the extent of weight loss achieved (12). Minor weight loss (<15%) was associated with a modest increase in total testosterone levels (by 2 nmol/L) and increases in SHBG (due to improvement in insulin resistance), while there was no increase in free testosterone levels at this degree of weight loss (13). Several clinical trials have evaluated the impact of bariatric surgery on testosterone levels in men, showing an increase in testosterone levels following the procedure, which is more efficient in achieving weight loss than a low-calorie diet (14). Lifestyle modifications resulted in a mean weight loss of 9.8%, with an increase in total testosterone of 2.9 nmol/L. In contrast, bariatric surgery achieved a mean weight loss of 32% with an increase in total testosterone of 8.7 nmol/L (15).

The role of testosterone treatment in middle-aged to older men with FH remains debatable and controversial because definitive clinical trials designed and powered to provide conclusive evidence regarding long-term health benefits and potential risks of testosterone therapy (TTh) are currently lacking (1, 2). There is a good evidence from larger randomized

clinical trials that TTh improves sexual symptoms in hypogonadal men with MetS and/or T2D (16–19). Long-term TTh in 823 hypogonadal males (among which 57.6% were obese) showed that 11 years of therapy improved body weight, waist circumference, and body mass index, along with a significant increase in testosterone levels (8.5 ± 0.2 nmol/L). TTh also decreased fasting blood glucose and glycated hemoglobin (HbA1c) and improved lipid profiles (20). Another study showed that TTh achieved a statistically significant reduction in fat mass, increase in lean body mass, and HbA1c improvement associated with a 52% improvement in beta-cell function (21). A small randomized controlled trial involving 16 subjects with newly diagnosed T2D and MetS demonstrated that the combination of TTh and lifestyle interventions led to greater therapeutic improvements in glycemic control and reversed MetS condition after 52 weeks of treatment compared with lifestyle interventions alone (9).

Other benefits of TTh include improvement in libido and erectile function, volumetric vertebral and femoral mineral bone density, body composition, anemia, energy, and motivation, and also reduce arterial stiffness, intraabdominal and intramuscular fat, and bone remodeling, which are added advantages to the treatment of symptoms of testosterone deficiency (2, 22–25). Low testosterone may contribute to poor motivation to initiate healthy lifestyle interventions. Few studies have shown that TTh may increase motivation to diet and exercise (1, 26). In addition, long-duration epidemiological studies have found that TTh reduced mortality in T2D (27).

In some men, measures to reverse FH may be unsuccessful, either because the implementation of treatment is not feasible (e.g. cessation of opioids in chronic pain or antiretroviral therapy for HIV) or they are not achieved or maintained (e.g. sustained weight loss in obese patients). Even if successful, such measures may be insufficient to relieve symptoms and normalize testosterone levels. In these men, testosterone treatment could be started concomitantly or after these initial measures fail (1). Guidelines suggest a trial testosterone treatment for no less than six months in these men to determine whether there is a clinical benefit of TTh. The Testosterone Trials clearly showed improvement of most symptoms of FH within three months of initiation of testosterone treatment and recovery of testosterone concentrations to the mid-normal range (28). When there

is no clinical improvement after six months of sufficient testosterone replacement, TTh should be discontinued, and other causes of symptoms or alternate testosterone modalities should be considered (1, 3, 8).

Whenever testosterone treatment is considered, contraindications must first be excluded. TTh is contraindicated in men with untreated prostate and breast cancer, as well as severe heart failure and recent major acute CV events. Severe low urinary tract symptoms and hematocrit >48–50% are relative contraindications for TTh (3, 8, 29). The patient should be fully informed of potential risks prior to agreeing on the treatment.

The follow-up of the testosterone treatment in patients with FH is regulated by recommendations made in the Endocrine Society guidelines.

References

1. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. J Clin Endocrinol Metab. 2017;102(3)(3):1067–75.
2. Grossmann M, Jones TH. Functional hypogonadism in middle-aged and older men: testosterone treatment or not? Eur J Endocrinol. 2021;185(3):D1–9.
3. Corona G, Goulis DG, Huhtaniemi I, Zitzmann M, Toppari J, Forti G, et al. European Academy of Andrology (EAA) guidelines on investigation, treatment and monitoring of functional hypogonadism in males. Andrology. 2020;8(5):970–87.
4. Louters M, Pearlman M, Solsrud E, Pearlman A. Functional hypogonadism among patients with obesity, diabetes, and metabolic syndrome. Int J Impot Res [Internet]. 2021 Nov 13; Available from: https://doi.org/10.1038/s41443-021-00496-7
5. Hall SA, Esche GR, Araujo AB, Travison TG, Clark RV, Williams RE, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab. 2008;93(10):3870–7.
6. Calderón B, Gómez-Martín JM, Vega-Piñero B, Martín-Hidalgo A, Galindo J, Luque-Ramírez M, et al. Prevalence of male secondary hypogonadism in moderate to severe obesity and its relationship with insulin resistance and excess body weight. Andrology. 2016;4(1):62–7.

7. Martits A, Costa E, Nardi A, Nardozza Jr A, Faria G, Facio Jr F, et al. Late-onset hypogonadism or ADAM: diagnosis. Rev Assoc Médica Bras. 2014;60:286–94.
8. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an Endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715–44.
9. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl. 2013;30(6):726–33.
10. Reis LO, Favaro WJ, Barreiro GC, De Oliveira LC, Chaim EA, Fregonesi A, et al. Erectile dysfunction and hormonal imbalance in morbidly obese male is reversed after gastric bypass surgery: a prospective randomized controlled trial. Int J Androl. 2010;33(5):736–44.
11. KLIBANSKI A, BEITINS IZ, BADGER T, LITTLE R, MCARTHUR JW. Reproductive Function during Fasting in Men*. J Clin Endocrinol Metab. 1981;53(2):258–63.
12. Tajar A, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, Lee DM, et al. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European male aging study (EMAS). J Clin Endocrinol Metab. 2012;97(5)(5):1508–16.
13. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab. 2011;96(8):2341–53.
14. Alagna S, Cossu ML, Gallo P, Tilocca PL, Pileri P, Alagna G, et al. Biliopancreatic diversion: long-term effects on gonadal function in severely obese men. Surg Obes Relat Dis. 2006;2(2):82–6.
15. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol. 2013;168(6):829–43.
16. Jones TH, Arver S, Behre HM, Buvat J, Meuleman E, Moncada I, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care. 2011;34(4):828–37.
17. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, et al. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. 2014;11(3):840–56.
18. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren Louis J. G., Giltay Erik J., Saad Farid. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf). 2010;73(5):602–12.

19. Yassin AA, Alwani M, Talib R, Almehmadi Y, Nettleship JE, Alrumaihi K, et al. Long-term testosterone therapy improves liver parameters and steatosis in hypogonadal men: a prospective controlled registry study. Aging Male. 2020;23(5):1553–63.

20. Saad F, Doros G, Haider KS, Haider A. Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: real-world data from a controlled registry study. Int J Obes 2005. 2020;44(6):1264–78.

21. Dimitriadis GK, Randeva HS, Aftab S, Ali A, Hattersley JG, Pandey S, et al. Metabolic phenotype of male obesity-related secondary hypogonadism pre-replacement and post-replacement therapy with intra-muscular testosterone undecanoate therapy. Endocrine. 2018;60(1):175–84.

22. Corona G, Giagulli VA, Maseroli E, Vignozzi L, Aversa A, Zitzmann M, et al. Therapy of endocrine disease: Testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol. 2016;174(3):R99–116.

23. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, Ellenberg SS, Cauley JA, Ensrud KE, et al. Effect of Testosterone Treatment on Volumetric Bone Density and Strength in Older Men With Low Testosterone: A Controlled Clinical Trial. JAMA Intern Med. 2017;177(4):471–9.

24. Vlachopoulos C, Ioakeimidis N, Miner M, Aggelis A, Pietri P, Terentes-Printzios D, et al. Testosterone deficiency: A determinant of aortic stiffness in men. Atherosclerosis. 2014;233(1):278–83.

25. Haider A, Gooren LJG, Padungtod P, Saad F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. Exp Clin Endocrinol Diabetes. 2010;118(3):167–71.

26. Watts NB, Adler RA, Bilezikian JP, Drake MT, Eastell R, Orwoll ES, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802–22.

27. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013;169(6):725–33.

28. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Lessons from the testosterone trials. Endocr Rev. 2018;39(3):369–86.

29. Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC, et al. European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. Eur Urol 2021;80(5):603–620.

DIABETIC FOOT SCREENING FROM 1996 TO 2022: MESSAGES FROM THE DATA-BASE

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Foot ulcers, gangrene and amputation are among the most feared complications of diabetes mellitus that also importantly influence the quality of life. They pose a huge burden on the patient and his relatives as well as on the healthcare system (1). Many foot complications can be prevented by interdisciplinary approach, which includes early detection of high-risk patients, treatment of foot ulcers, rehabilitation and prevention of recurrence (2–5).

The International Working Group on the Diabetic Foot (IWGDF) has recommended an annual examination of people with diabetes at very low risk of foot ulceration (IWGDF risk 0) to screen for developing risk factors (history of foot ulcer, foot deformity, loss of protective sensation, absent pedal pulses) (6). The recommendation of at least 12-month interval of screening is in line with the view of other scientific societies (7) and is largely based on the general expert consensus rather than on strong clinical evidence. A large proportion of people with diabetes do not receive proper screening due to insufficiencies in health care resources even in developed countries (8).

Structured diabetic foot care in Slovenia started around the year 1990; in January 1995 a National working group on the diabetic foot was established, a national foot screening protocol was adopted in July 1995.

Out-patient diabetes clinic in Ljubljana offers care to approximately 9,500 registered patients with diabetes. Diabetic foot clinic was established in January 1990. At the beginning, it was running once weekly but gradually expanded into full-time service, running daily from Monday to Friday, in two rooms with 4 examination desks, two full-time and one part-time nurse and one doctor – consultant (specialist in internal medicine – diabetology). The activities of the foot clinic are both preventative and curative: foot screening, ankle-brachial index measurement, education about foot care, wound care and research. Interdisciplinary approach is well established, the cooperation with surgery and angiology department is running smoothly.

Regular foot screening was introduced in November 1996. A computerized data base in a form of an Excel file was created at the very beginning and all data obtained have been recorded. There was no overwriting of the entries, the findings of successive foot examinations were entered into successive file sheets. In this way, the file currently contains 25 sheets as 4 patients have had 25 foot examinations during the course of 27 years. According to the recommendations of IWGDF [6], at least 9,500 foot screening procedures should be performed every year – on average 36 on every of the 260 working days – which is absolutely unfeasible with the available resources. In the period from November 1996 till end of August 2022, 40,634 foot screenings were done, on average 1,505 per year. At least one foot examination was done in 15,812 patients. The number of follow-up screening procedures is much smaller, with less than 1,000 patients being examined 8 times or more and less than 100 patients 15 times or more. The average number of first foot examinations is less than 600 per year. This number was higher in the first years when we had to screen the whole population attending the clinic. Later on, the majority of the patients are screened immediately after the diagnosis of diabetes is confirmed. The detailed figures on the work done are shown in Tables 1, 2 and 3.

Slovenian foot screening protocol follows the recommendations from the IWGDF guideline, the only difference is the risk status classification:

1 – normal sensation, no deformity; 2 – loss of protective sensation, no deformity; 3 – ischemia without deformity or sensory loss; 4 – combination of sensory loss and/or deformity and/or absent pedal pulses; history of foot ulcer; Charcot foot. Adoption of the IWGDF classification is planned in January 2023.

TABLE 1:

The number of successive foot examinations between 1996 and 2022.

	N
1st examination	15,812
2nd examination	8,053
3rd examination	5,163
4th examination	3,419
5th examination	2,336
6th examination	1,631
7th examination	1,162
8th examination	840
9th examination	621
10th examination	469
11th examination	313
12th examination	231
13th examination	165
14th examination	114
15th examination	82
16th examination	58
17th examination	45
18th examination	39
19th examination	22
20th examination	18
21st examination	14
22nd examination	10
23rd examination	7
24th examination	6
25th examination	4
Total	**40,634**
Average/year	**1,505**

TABLE 2:
Summary of the findings at the first foot examination (total 15,812 records).

	N	%
History of foot ulcer	683	4,3
Symptoms of neuropathy	6829	43,2
Foot deformity	8877	56,1
Open ulcer	945	6,0
Loss of protective sensation	2511	16,5
Absent pedal pulses	1151	7,6

TABLE 3:
Risk status classification at the first foot examination (total 15,812 records).

Risk group	N	%
1	9812	62,1
2	2011	12,7
3	0257	1,6
4	3732	23,6

An interesting observation is the number of referrals to vascular specialist. During the first three years, we have had over 100 referrals per year, later this number dropped to values between 20 in 25, representing approximately 5% of the screened patients. The higher numbers in the first years may be due to longer duration of diabetes at the time of first foot examination.

The messages

Diabetic foot screening not only reveals the patients who are at risk of developing foot ulceration but also provides a comprehensive overview of foot pathology in the observed population. Annual screening of the whole population is not feasible because of limited resources. A risk prediction model which would enables stratification of individuals based on likelihood of complications is urgently needed because it would enable extending the frequency for screening of those with low risk, thus freeing up resources for those with higher foot ulcer risk (9).

References

1. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res. 2020;13(1):16.
2. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA, et al. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3266.
3. Monteiro-Soares M, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, et al. Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3273.
4. Rayman G, Vas P, Dhatariya K, Driver V, Hartemann A, Londahl M, et al. Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3283.
5. Bus SA, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, et al. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3269.
6. Schaper NC, van Netten JJ, Apelqvist J, et al. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36 Suppl 1:e3266.
7. Formosa C, Gatt A, Chockalingam N. A Critical Evaluation of Existing Diabetic Foot Screening Guidelines. Rev Diabet Stud. 2016;13(2-3):158-186.
8. Chevreul K, Berg Brigham K, Bouché C. The burden and treatment of diabetes in France. Global Health. 2014;10:6.
9. Štotl I, Blagus R, Urbančič-Rovan V. Individualised screening of diabetic foot: creation of a prediction model based on penalised regression and assessment of theoretical efficacy. Diabetologia. 2022;65(2):291-300.

SCREENING OPTIMIZATION USING PREDICTIVE MODELS

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Diabetic foot disease poses a huge burden on the people with diabetes, including their family, health care system, and society in general (1). Strategies that include elements of screening, prevention, patient and staff education, and interdisciplinary treatment can reduce the load of diabetic foot disease on individual and public level (2). However, implementation of the guidelines and the establishment of multidisciplinary clinics for holistic management of diabetic foot disorders varies and remains sub-optimal (1).

Self-assessment of diabetes-related foot problems is unreliable, and self-perceived foot health should be assessed together with foot examination findings (3). Therefore, the International Working Group on the Diabetic Foot (IWGDF) has recommended an annual examination of people with diabetes at very low risk of foot ulceration (IWGDF risk 0) to screen for developing risk factors (2). The recommendation of at least 12 months interval of screening is in line with the view of other scientific societies (4) and is largely based on the general expert consensus and on the results of the study of Litzelman et al. (5) that did not directly address the question of different lengths of the screening interval.

A large proportion of people with diabetes do not receive proper screening due to insufficiencies in health care resources, even in developed countries. It was estimated that only 20% of people with diabetes are being screened with a monofilament according to ENTRED study in France (6). A multicenter, epidemiological, cross-sectional study from Fernandez et al. (7) that examined clinical records of 443 people with type 2 diabetes in primary care in Spain, showed poor diabetic foot screening compliance (performed in 37%) and infrequent ulcer risk stratification (performed in 12.4%). According to the Scottish Diabetes Survey from 2019, 56.7% of people with type 1 and 64.8% with type 2 diabetes had their foot scores recorded within 15 months (8).

The probability of foot complications among persons with diabetes can show substantial individualized variability and within different populations (9). This variation is not addressed efficiently with current recommendations that propose fixed and arbitrary screening frequency (10). Screening interval is increasingly recognized as a public health blind spot that offers many opportunities for improvement of healthcare (10). A clinical prediction model could be used to tailor the frequency of screening for each person based on individual probability of complications at the time of screening.

Creation of a proof of the concept organizational model

Our study group has developed a prediction model for diabetic foot complications that shows good discrimination ability with cross-validated AUC of 0.84 for LOPS (loss of peripheral sensation) and 0.80 for LPP (loss of peripheral pulses) (11). The majority of foot screenings not unsurprisingly are performed on patients with low risk at our clinic. Additionally, the risk for foot complications over years seems to increase more slowly in people with low baseline risk than in their high baseline risk counterparts, therefore identification of low risk sub-population presents an opportunity for optimizing the screening process.

As a proof of the concept, we have created a simplified organizational model for screening of subjects with IWGDF risk 0 and based on individualized probability for LPP and LOPS (11). The potential for biennial rather than annual screening, for subjects stratified as IWGDF group 0 and a low probability of complications (using 5% and 10% threshold), was estimated. The decision about the alternative biennial screening interval duration in case of low risk was arbitrary and was based on the local estimate of total numbers of screenings needed, that would be manageable at our clinic.

The individual probability estimation needed for the organizational model was calculated on patient population of our clinic. In this proof of the concept study, we could demonstrate a 26.5% (cut-off: 5% risk) to 40.5 % (cut-off: 10% risk) reduction of absolute number of screenings needed for population with IWGDF risk 0 in two year period, when the screening interval was extended biennially instead of annually in the low-risk group. Reduction was even more pronounced when the model was tested with IWGDF 0 group without foot deformities.

Reduction of screenings in 2 years in IWGDF risk group 0		
Probability cut-off	5%	10%
All screenings	26.5%	40.5%
Without foot deformity	36.9%	46.8%

Currently, the patients with diabetes at our center are not screened according to the guidelines, predominantly due to insufficient capacity and only partial insurance reimbursement. Introduction of the framework that proposes fewer examinations than currently advised by guidelines would paradoxically increase the absolute numbers of screenings performed in patients with IWGDF risk 0 at our center, therefore, safety and efficiency may improve.

Conclusions

Diabetes related burden for health care systems is increasing with aging populations, increasing diabetes prevalence and obesity worldwide.

Improvements in health care systems are urgently needed to enable adequate care for people with diabetes that is often not optimal because of lack of systemic resources.

A protocol for diabetic foot screening that is enhanced by risk prediction model enables stratification of individuals based on likelihood of complications. Discrimination of low ulcer risk could extend the frequency for screening those with low risk, thus freeing up resources for those with higher foot ulcer risk. The proposed model requires further refinement and external validation, but it also shows the potential for improving compliance with guidelines for screening which is often not appropriate.

References

1. van Acker K, Léger P, Hartemann A, Chawla A, Siddiqui MK. Burden of diabetic foot disorders, guidelines for management and disparities in implementation in Europe: a systematic literature review. Diabetes Metab Res Rev. 2014;30(8):635–45.
2. Schaper C, Van Netten JJ, Bus SA, Hinchliffe RJ, Apelqvist J, Lipsky BA. IWGDF Practical guidelines on the prevention and management of diabetic foot disease. IWGDF Practical Guidelines [Internet]. 2019; Available from: https://iwgdfguidelines.org/wp-content/uploads/2019/05/01-IWGDF-practical-guidelines-2019.pdf
3. Baba M, Foley L, Davis WA, Davis TME. Self-awareness of foot health status in patients with Type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabet Med. 2014;31(11):1439–45.
4. Formosa C, Gatt A, Chockalingam N. A Critical Evaluation of Existing Diabetic Foot Screening Guidelines. Rev Diabet Stud. 2016;13(2–3):158–86.
5. Litzelman DK, Slemenda CW, Langefeld CD, Hays LM, Welch MA, Bild DE, et al. Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. A randomized, controlled trial. Ann Intern Med. 1993;119(1):36–41.
6. Chevreul K, Berg Brigham K, Bouché C. The burden and treatment of diabetes in France. Global Health. 2014;10:6.
7. Evaluation of diabetic foot screening in Primary Care. - Abstract - Europe PMC [Internet]. [cited 2020 Dec 7]. Available from: https://europepmc.org/article/MED/24582291
8. Scottish Diabetes Data Group. Scottish Diabetes Survey 2019 [Internet]. 2020. Available from: https://www.diabetesinscotland.org.uk/wp-content/uploads/2020/10/Diabetes-Scottish-Diabetes-Survey-2019.pdf
9. Lu Y, Xing P, Cai X, Luo D, Li R, Lloyd C, et al. Prevalence and Risk Factors for Diabetic Peripheral Neuropathy in Type 2 Diabetic Patients From 14 Countries: Estimates of the INTERPRET-DD Study. Front Public Health [Internet]. Frontiers; 2020 [cited 2021 Mar 2];8. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2020.534372/full
10. Chiolero A, Anker D. Screening interval: a public health blind spot. Lancet Public Health. 2019; 4(4): e171–2.
11. Štotl I, Blagus R, Urbančič-Rovan V. Individualised screening of diabetic foot: creation of a prediction model based on penalised regression and assessment of theoretical efficacy. Diabetologia. 2022;65(2):291–300.

RADIOIODINE UPTAKE

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Eighty years have passed since radioactive iodine-131 (I-131) was successfully used to treat a hyperthyroid patient with Graves' disease in 1941. Since then, countless patients around the world have been diagnosed and treated for both benign and malignant thyroid disorders with different radioiodine isotopes (1).

The recognition and function of Na^+/I^- symporter

The ability of thyroid tissue to accumulate iodide (I^-), an essential ingredient of thyroid hormones, was recognized as early as 1896. However, the key protein involved in thyroid I^- uptake, Na^+/I^- symporter (NIS), was not discovered until 1996. NIS is a glycoprotein located on the basolateral surface of the thyrocyte. It mediates the active transport of I–into the cell against the electrical and chemical gradients (2). Since NIS cannot differentiate between non-radioactive and radioactive iodine, it provides a powerful tool for the diagnosis and treatment of thyroid disorders using

different radioiodine isotopes including iodine-123, -124, -125 and -131 (2). In addition to radioiodine, NIS also transports technetium-99m pertechnetate, a radiopharmaceutical commonly used in diagnostic procedures due to its wide availability (3).

Radioiodine uptake in thyroid depends on the activity and expression of NIS, both of which increase when thyrotropin receptor (TSHR) is stimulated. In Graves' disease, TSHR is stimulated by circulating stimulating antibodies, whilst in thyroid autonomous tissue the receptor is permanently activated due to a mutation. Our recent experience shows that in patients with Graves' disease and thyroid autonomous tissue, the 20-hour uptake of administered I-123 is 69% and 29%, respectively; in comparison to only 19% in euthyroid nodular goiter (4). TSHR can also be stimulated by the application of recombinant human thyrotropin, which is used in the treatment of euthyroid goiter or in the ablation of thyroid tissue following thyroid cancer surgery. In both cases the goal is to increase the uptake of I-131 and thus improve the success of treatment (3).

With increased iodine intake, the expression of NIS protein significantly decreases, which reduces uptake of radioiodine in the target thyroid tissue. This observation has been confirmed by several studies comparing I-131 uptake and its applied therapeutic activities before and after the increase in iodine supply. In Slovenia, for example, iodine concentration in kitchen salt was increased from 10 mg to 25 mg of potassium iodide per kg of salt in 1999. In the following years, the uptake of radioiodine in patients with autonomous tissue decreased by an average of 7% (from 45.3% to 31.0%), whilst the required therapeutic activity of I-131 increased by an average of 10% (from 713 MBq to 791 MBq) (5). Similarly, in Poland, where the iodine supply was increased in 1996, studies in Graves' patients demonstrated a 40% reduction in thyroid radioiodine uptake and a 40% increase in applied therapeutic activities of I-131 in subsequent years (6). In addition to increased iodine intake, destruction of thyroid tissue may also reduce the activity and expression of NIS. This may, for example, be observed in the hyperthyroid phase of Hashimoto's thyroiditis or postpartum thyroiditis. Finally, the action of NIS can also be affected by the competitive inhibitors thiocyanate and perchlorate. Perchlorate is therefore suitable for protection

against excessive iodine uptake in patients with thyroid autonomous tissue or Graves' disease who are candidates for short-term iodine overload (e.g. after the application of iodine contrast) (3).

Na^+/I^- symporter in extra-thyroidal tissues

NIS at mRNA and/or protein level is expressed in various extra-thyroidal tissues. Applying immunohistochemistry methods, NIS protein expression was shown in urinary bladder, colon, endometrium, kidney, prostate, and pancreas. However, plasma membrane immunopositivity was confirmed only in salivary ductal, gastric mucosa, and lactating mammary cells (7, 8). In salivary glands, stomach and intestine, NIS enables efficient absorption of I^- from the food; in salivary ductal cells (mainly in the parotid glands) and gastric mucosa cells, NIS is expressed on the basolateral membrane and contributes to the transfer of I^- from the bloodstream to the lumen of the gastrointestinal tract, and in the intestine, NIS is expressed on the apical membrane of the brush border of small intestine enabling transfer of I^- from the lumen into circulation (9).

In lactating mammary glands, abundant NIS expression on the basolateral membrane of the alveolar cells mediates the transfer of iodine from the blodstream into the milk to reach a concentration of approximately 150 µg/l. Stimulation of NIS expression during lactation is due to increased levels of various hormones, including oxytocin, prolactin, and estrogens (10, 11). In contrast, non-lactating normal breast tissue does not express NIS protein and is not able to accumulate I^-, unless pathological conditions such as hyperprolactinemia are present. NIS is also expressed in placental cells enabling transfer of I^- from maternal to fetal circulation. NIS mRNA and protein were also demonstrated in human testicular tissues, responsible for alterations in male patients undergoing radioioidine treatment for thyroid cancer (8).

Radioiodine therapy for thyroid and extra-thyroid tumors and future potentials

Radioiodine therapy is a validated treatment effective in benign thyroid diseases causing increased NIS expression and leading to hyperthyroidism, and in differentiated thyroid cancer after TSH-induced increased expression of NIS. For radioiodine refractory thyroid cancer, novel therapeutic approaches targeting the molecular pathways responsible for the loss of differentiation (and subsequent reduction of NIS) are being investigated. In the future, pharmacologic redifferentiation followed by radioiodine treatment might be one the main therapeutic strategies for such cancers (12).

The characterization of the molecular basis of I^- transport following the cloning of NIS, including its detection in some extrathyroidal tissues, has encouraged a large series of studies aiming to extend radioiodine treatment even to extrathyroidal tumors after induction of NIS expression (8). In this case, radioiodine uptake and concentration in normal thyrocytes needs to be blocked and selective downregulation of NIS expression and inhibition of organification by combination of T3 and methimazole has been described (13). Among the strategies explored to induce NIS expression in cancer cells, the transfer of NIS gene using vectors (mainly viruses) and constructs able to ensure selective expression in tumor cells or stimulation of the expression of a functional endogenous NIS have been reported (8). At the preclinical level, significant progress has been made in the development of the NIS gene therapy concept, from local NIS gene delivery to new applications in disseminated disease, such as the use of oncolytic viruses, non-viral polyplexes, and genetically engineered mesenchymal stem/stromal cells (14).

References

1. Fahey FH. Celebrating eighty years of radionuclide therapy and the work of Saul Hertz. J Appl Clin Med Phys. 2021; 22 (1): 4–10.
2. Portulano C, Paroder-Belenitsky M, Carrasco N. The Na+/I– Symporter (NIS): Mechanism and Medical Impact. Enodocr Rev. 2014; 35 (1): 106–149.
3. De la Vieja A, Riesco-Eizaguirre G. Radio-iodide treatment: from molecular aspects to the clinical view. Cancers. 2021; 13 (5): 995.
4. Rot Ž, Zaletel, T, Krković D, Gaberšček S, Zaletel K. The incidence of radioiodine-induced Graves' disease following treatment of thyroid autonomous tissue. Eur J Nucl Med Mol Imaging. 2021; 48 (1): S381.
5. Gaberšček S, Bajuk V, Zaletel K, Pirnat E, Hojker S. Beneficial effects of adequate iodine supply on character¬istics of thyroid autonomy. Clin Endocrinol (Oxf). 2013; 79: 867–873.
6. Baczyk M, Junik R, Ziemicka K, Sowinski J. Iodine prophylaxis intensification. Influence on radioiodine uptake and activity of 131I used in the treatment of hyperthyroid patients with Graves' disease. Nuklearmedizin. 2005; 44: 197–199.
7. Bruno R, Giannasio P, Ronga G, Baudin E, Travagli JP, Russo D, et al. Sodium iodide symporter expression and radioiodine distribution in extrathyroidal tissues. J Endocrinol Invest. 2004; 27 (11): 1010–1014.
8. Micali S, Bulotta S, Puppin C, Territo A, Navarra M, Bianchi G, et al. Sodium iodide symporter (NIS) in extrathyroidal malignancies: focus on breat and urological cancer. BMC Cancer. 2014, 14: 303–315.
9. Nicola JP, Basquin C, Portulano C, Reyna-Neyra A, Paroder M, Carrasco N. The Na+/I-symporter mediates active iodide intake in the intestine. Am J Cell Physiol. 2009; 296: C654–C662.
10. Tazebay UH, Wapnir IL, Levy O, Dohan O, Zuckier LS, Zhao QH, et al. The mammary gland iodide transporter is expressed during lactation and in breast cancer. Nat Med. 2000; 6: 871–878.
11. Cho JY, Leveille R, Kao R, Rousset B, Parlow AF, Burak WEJ, et al. Hormonal regulation of radioiodide uptake activity and Na+/I- symporter expression in mammary glands. J Clin Endocrinol Metab. 2000; 85: 2936.
12. Oh JM, Ahn BC. Molecular mechanisms of radioactive iodine refractoriness in differenetiated thyroid cancer: Impaired sodium iodide symporter (NIS) expression owing to altered signaling pathway activity and intracellular localization of NIS. Theranostics. 2021; 11 (13): 6251–6277.

13. Wapnir IL, Goris M, Yudd A, Dohan O, Adelman D, Nowels K, et al. The Na+/I- symporter mediates iodide uptake in breast cancer metastases and can be selectively down-regulated in the thyroid. Clin Cancer Res. 2004; 10 (13): 4294–4302.

14. Spitzweg C, Nelson PJ, Wagner E, Bartenstein P, Weber WA, Schwaiger M, et al. The sodium iodide symporter (NIS): novel applications for radionuclide imaging and treatment. Endocr Relat Cancer. 2021; 28 (10): T193–T213.

RADIOIODINE THERAPY

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Introduction

^{131}I is a beta-emitting radionuclide used for the treatment of thyroid disorders. ^{131}I decays to stable ^{131}Xe, has a physical half-life of 8.02 days, a principal gamma ray of 364 keV, a principal beta particle with a maximum energy of 0.807 MeV and average energy of 0.192 MeV. Beta particles have an average range in tissue of 0.4 mm and the maximum range of about 3 mm. Radiobiological effects of radioiodine on tissues are direct (damage to DNA) or indirect through the production of free radicals that react with critical macromolecules (1).

Hertz and Roberts (Massachusetts General Hospital, USA) used the radioiodine for the first time for the treatment of the hyperthyroidism on March 31, 1941. In 1946 the results of two different scientific studies were published in the same issue of the Journal of the American Medical Associations (JAMA) and they both announced the radioiodine therapy as successful treatment for hyperthyroidism (2). The scientific studies of the long-term risk of cancer and other adverse effects after radioiodine treatment also began at that time (2,3).

Radioiodine therapy is today an established treatment for benign thyroid disease with procedure guidelines by European Association of Nuclear Medicine (EANM), regulated by European Commission directives and local regulations and policies based on the recommendations of the International Commission on Radiological Protection (ICRP) (1, 4).

Indications for the radioiodine therapy

In our article, we will discuss the radioiodine treatment of benign thyroid disorders. Indications for the radioiodine treatment are Graves' disease, toxic multinodular goitre, solitary hyperfunctioning nodule, nontoxic multinodular goitre and goitre recurrence. There are two methods to determine the activity of 131I: estimation (based on the volume of the gland, the so-called "fixed dose") and calculation (based on radioiodine uptake measurements) (1). The range of activities of ^{131}I currently prescribed in our tertiary centre is between 350 and 925 MBq.

Graves' disease is a systemic autoimmune disorder caused by stimulating antibodies acting as an agonist on the thyrotropin-receptor (TSH-R) on thyroid follicular cells and other TSH-R-expressing tissues. This leads in thyroid to hyperplasia and unregulated thyroid hormone production and secretion. Inflammatory changes in orbital tissue (Graves' orbitopathy - GO) are present in more than half of patients. Patients with newly diagnosed Graves' hyperthyroidism are usually treated with antithyroid drugs. Radioiodine therapy is often recommended for patients with side-effects or allergy to antithyroid drugs, recurrence of the disease after a course of antithyroid drugs, exacerbation of GO and in older patients who have had atrial fibrillation, cardiac failure, or cardiac ischemic symptoms precipitated by hyperthyroidism. Radioiodine therapy or thyroidectomy may be also considered in patients with newly diagnosed Graves' hyperthyroidism that prefer this approach. Most patients become hypothyroid following the radioiodine therapy (5,6).

Toxic multinodular goitre and solitary hyperfunctioning nodule (toxic adenoma) are the result of diffuse or focal hyperplasia of thyrocytes, which have the ability to function autonomously without TSH (7). Toxic multinodular goitre and toxic adenoma can cause subclinical hyperthyroidism (8). Despite the normal free thyroxine and total or free triiodothyronine levels, patients often report palpitations, nervousness, tremor, heat intolerance and sweating, which affects their quality of life (8,9). Subclinical hyperthyroidism is associated with an increased risk for atrial fibrillation (10) and ischemic heart disease (11, 12). The risk is higher for TSH level lower than 0.10 mIU/L (11). There is an increased risk for osteoporotic fractures in postmenopausal women, especially those with a TSH level lower than 0.10 mIU/L (13, 14), and according to recent studies, also for dementia in the elderly (15). Overt hyperthyroidism occurs after excessive iodine intake (16,17).

When considering treating toxic multinodular goitre and solitary hyperfunctioning nodule with radioiodine, our decision is based on the severity of the subclinical hyperthyroidism, age and presence of symptoms and co-morbidities (17). The aim of the radioiodine treatment is the destruction of autonomously functioning tissue and achievement of the euthyroidism (7).

Surgery is considered standard therapy for large nontoxic goitre. Radioiodine treatment is indicated in patients with medical contraindications to thyroid surgery, especially cardiopulmonary diseases, and patients who wish to avoid surgery. In patients with large nontoxic goitre causing compressive symptoms surgical treatment is indicated (1, 18, 19).

Side effects of radioiodine treatment

The optimal activity for the radioiodine treatment of benign thyroid disorders is determined either by estimation or by calculation but always in respect of the principle that exposure to radiation have to be "as low as reasonably achievable" (ALARA) (20, 21).

Absolute contraindications for radioiodine treatment are pregnancy and breastfeeding. Relative contraindications are severe hyperthyroidism and active GO (1, 22). The patient has a discussion with a qualified medical

doctor before radioiodine treatment; has to be familiar with the protective measures in radiation safety and has to sign an informed consent for the treatment (4, 23).

There are relatively few side effects from the treatment. In the first weeks after the application of radioiodine treatment patients with a large goitre may notice transient swelling of the goitre, there may be a transient raise in free T4 and free T3 levels and the GO can worsen (1, 3). The incidence of radiation thyroiditis after radioiodine treatment of hyperthyroidism is approximately 1% (24). Among the acute side effects there are no gastrointestinal symptoms, signs of bone marrow suppression or sialadenitis, that occur at higher levels of administered dose used to treat thyroid cancer (1, 3, 25).

The main side effect of radioiodine treatment is hypothyroidism and its incidence continues to increase over time. In 5% of the patients treated with radioiodine for toxic multinodular goitre or solitary hyperfunctioning nodule Graves' disease occurs (26). Studies have shown no effect on fertility or possible teratogenic effects in case of subsequent pregnancy (1, 3). There are several cohort studies on cancer risks after radioiodine treatment of hyperthyroidism. The selected patients for the studies were treated with radioiodine from 1946 onward. The studies found that radiation-induced cancer risks are small and may only be detectable at higher levels of administered dose (27).

Conclusions

Radioiodine treatment of benign thyroid disease has an 80-year long history. The treatment is accessible, effective and safe. We can ensure additional safety by carefully selecting patients for the radioiodine treatment, by additional diagnostics, with patient education and with precise treatment planning.

References

1. Stokkel M, Handkiewicz Junak D, Lassmann M, Dietlein M, Luster M. EANM procedure guidelines for therapy of benign thyroid disease. Eur J Nucl Med Mol Imaging. 2010; 37(11): 2218-28.
2. Sawin C, Becker D. Radioiodine and the treatment of hyperthyroidism: the early history. Thyroid. 1997; 7(2): 163-76.
3. Bonnema SJ, Hegedüs L. Radioiodine Therapy in Benign Thyroid Diseases: Effects, Side Effects, and Factors Affecting Therapeutic Outcome. Endocrine Reviews. 2012; 33(6): 920–980
4. Beckers C. Regulations and policies on radioiodine 131I therapy in Europe. Thyroid. 1997; 7(2): 221-224.
5. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018; 7(4): 167-186.
6. Fanning E, Inder WJ, Mackenzie E. Radioiodine treatment for graves' disease: a 10-year Australian cohort study. BMC Endocr Disord. 2018;18(1):94.
7. Krohn K, Paschke R. Progress in Understanding the Etiology of Thyroid Autonomy. J Clin Endocrinol Metab. 2001; 86(7): 3336-45.
8. Santos Palacios S, Pascual-Corrales E, Galofre JC. Management of subclinical hyperthyroidism. Int J Endocrinol Metab. 2012; 10(2): 490-496.
9. Biondi B, Palmieri EA, Fazio S, Cosco C, Nocera M, Saccà L. et. al. Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. J Clin Endocrinol Metab. 2000; 85(12):4701-5.
10. Auer J, Scheibner P, Mische T, Langsteger W, Eber O, Eber B. Subclinical hyperthyroidism as a risk factor for atrial fibrillation. J Auer et al. Am Heart J. 2001; 142(5): 838-42.
11. Collet TH, Gussekloo J, Bauer DC, et al. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med. 2012; 172(10): 799-809.
12. Sohn SY, Lee E, Lee MK, Lee JH. The Association of Overt and Subclinical Hyperthyroidism with the Risk of Cardiovascular Events and Cardiovascular Mortality: Meta-Analysis and Systematic Review of Cohort Studies. Endocrinol Metab (Seoul). 2020; 35(4): 786-800.
13. Blum MR, Bauer DC, Collet TH, et al. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. JAMA. 2015; 313(20): 2055-2065.

14. Vendrami C, Marques-Vidal P, Gonzalez Rodriguez E, Hans D, Waeber G, Lamy O. Thyroid-stimulating hormone is associated with trabecular bone score and 5-year incident fracture risk in euthyroid postmenopausal women: the OsteoLaus cohort. Osteoporos Int. 2022; 33: 195–204.

15. Joy Mathew C, Jose MT, Elshaikh AO, Shah L, Lee R, Cancarevic I. Is Hyperthyroidism a Possible Etiology of Early Onset Dementia?. Cureus. 2020;12(9):e10603. Published 2020 Sep 22.

16. Leung AM, Braverman LE. Iodine-induced thyroid dysfunction. Curr Opin Endocrinol Diabetes Obes. 2012; 19(5): 414-419.

17. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on Diagnosis and Treatment of Endogenous Subclinical Hyperthyroidism. Eur Thyroid J 2015; 4: 149-163.

18. Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Søe-Jensen P, Hansen JM. Radioiodine treatment of multinodular non-toxic goitre. BMJ. 1993; 307(6908):828-32.

19. Huysmans D, Hermus A, Edelbroek M, Barentsz J, Corstens F, Kloppenborg P. Radioiodine for nontoxic multinodular goiter. Thyroid. 1997; 7(2): 235-9.

20. Van Isselt JW, De Klerk JMH, Lips CJM. Radioiodine treatment of hyperthyroidism: fixed or calculated doses; intelligent design or science?. Eur J Nucl Med Mol Imaging. 2007; 34: 1883–1884.

21. Pravilnik o pogojih za uporabo virov ionizirajočih sevanj v zdravstvu (Uradni list RS, št. 111/03, 75/15, 76/17 – ZVISJV-1 in 33/18) [citirano 27.06.2022]. Dosegljivo na http://www.pisrs.si/Pis.web/pregledPredpisa?id=PRAV4561

22. Padda IS, Nguyen M. Radioactive Iodine Therapy. StatPearls Publishing; 2022 [citirano 27.06.2022]. Dosegljivo na: https://www.ncbi.nlm.nih.gov/books/NBK557741/

23. Lazarus JH. Guidelines for the use of radioiodine in the management of hyperthyroidism: a summary. Prepared by the Radioiodine Audit Subcommittee of the Royal College of Physicians Committee on Diabetes and Endocrinology, and the Research Unit of the Royal College of Physicians. J R Coll Physicians Lond. 1995; 29(6): 464-469.

24. Mizokami T, Hamada K, Maruta T, Higashi K, Tajiri J. Painful Radiation Thyroiditis after 131I Therapy for Graves' Hyperthyroidism: Clinical Features and Ultrasonographic Findings in Five Cases. Eur Thyroid J. 2016; 5(3): 201-206.

25. Sánchez Barrueco A, González Galán F, Alcalá Rueda I, Santillán Coello JM, Barrio Dorado MP, Villacampa Aubá JM et. al. Incidence and risk factors for radioactive iodine-induced sialadenitis, Acta Oto-Laryngologica. 2020; 140(11): 959-962.

26. Nygaard B, Faber J, Veje A, Hegedüs L, Hansen JM. Transition of nodular toxic goiter to autoimmune hyperthyroidism triggered by 131I therapy. Thyroid. 1999; 9(5): 477-81.

27. Shim SR, Kitahara CM, Cha ES, Kim S, Bang YJ, Lee WJ. Cancer Risk After Radioactive Iodine Treatment for Hyperthyroidism: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021; 4(9):e2125072.

RADIOIODINE AND GRAVES' ORBITOPATHY

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Radioiodine (RAI) treatment of Graves' disease (GD) is reported to be a risk factor for the occurrence or worsening of Graves' orbitopathy (GO) in up to 20% of patients (1), which can be prevented with glucocorticoids. The optimal glucocorticoid regimen, however, is yet to be determined (2). The 2021 European Group on Graves' orbitopathy (EUGOGO) recommends the administration of oral prednisone or prednisolone prophylaxis to patients treated with RAI who are at risk of development or progression of GO (smoking, high serum level of thyrotropin receptor antibodies, severe hyperthyroidism, preexisting GO). The proposed regimen for high-risk patients is a starting dose of 0.3–0.5 mg/kg/body weight, tapered, and withdrawn after 3 months. The recommendation for low-risk patients is 0.1–0.2 mg/kg/body weight of prednisone/prednisolone, tapered, and withdrawn after 6 weeks. Patients with a stable inactive GO and without any risk factors for GO progression can receive RAI without prednisone/prednisolone cover (3).

At the Department of Nuclear Medicine, UMC Ljubljana, patients with GD are often offered treatment with RAI. Patients with mild active GO preventatively receive a short dose of oral methylprednisolone (96 mg on the 1st, 3rd, and 5th day) concomitant to RAI. Patients with moderate-to-severe and active GO receive longer regimens of oral methylprednisolone for three weeks, starting with 96 mg every second day, gradually tapering weekly for 32 mg. In patients with more severe GO and risk factors for its progression, we administer methylprednisolone intravenously with weekly doses of 500 mg for one to two months, followed by weekly doses of 250 mg for one month; a cumulative dose of 3000-5000 mg.

In a recent dissertation (4) we retrospectively evaluated the beneficial effects of our glucocorticoid regimens prophylaxis given concomitantly with RAI, for the prevention of the occurence or worsening of GO. We also analyzed the connection between the duration of GO activity and RAI treatment, as well as the risk factors for the occurence of GO after RAI treatment. The study included 724 patients who were diagnosed with GD for the first time during the years 2005-2009 and were later treated with RAI. Among them, 75.8 % (N=549) did not receive glucocorticoid prophylaxis as they did not have GO. These patients represented the control group; among them, only 3.8 % developed GO after RAI which is comparable with published data (5). Patients with mild GO and patients at risk for the development of GO (N=142, 19.6 %) were given a short dose of methylprednisolone prophylaxis concomitantly with RAI treatment; only 4% of them experienced worsening of GO which was statistically insignificant compared to the control group. This showcases a beneficial effect of our short-dose methylprednisolone regimen with RAI for the prevention of the occurrence or worsening of GO. A group of patients with moderate-to-severe active GO (N=33, 4.6 %) received longer regimens or intravenous methylprednisolone concomitantly with RAI; none of the patients from this group experienced a worsening of GO. Furthermore, in most of them (N=30, 90.9 %) GO improved after the treatment. That implies that the RAI treatment with appropriate glucocorticoid prophylaxis is also safe in patients with moderate-to-severe GO. Patients who received RAI in 6 months or fewer from the onset of GD, showed a significantly shorter duration of GD activity compared to patients who received RAI more than 6 months after the onset of GD (7.8±4.4 months vs. 9.5±5.1 months, p=0.032); this shows the importance of timely RAI treatment. As the duration of GO activity was also significantly longer before RAI than after RAI (6.5±4.2 months vs. 2.2±3.3 months, p<0.001), the RAI treatment in patients with active GO should be given with concomitant steroids soon after medical management of hyperthyrosis.

Regarding possible risk factors for GO after RAI (N=552) we concluded that it is important to administer the correct RAI dosage for a successful first treatment of GD. A greater proportion of patients who did not develop GO after RAI therapy were successfully treated with the first RAI dose (92 % vs 74 %, p =0.008) and were less likely to require a third RAI dose (0.2 % vs 8.7 %, p<0,001) than patients who developed GO after RAI therapy.

According to our study, the presence of GO at GD presentation or anytime before but not during RAI treatment is also a risk factor for GO occurrence after RAI (3.8 % vs 13 % or 21.7 %, p=0.030 or p<0.001).

In our study cohort of 171 patients with GO at the time of RAI, GO worsened in only 5 patients after RAI therapy with concomitant steroids treatment, whereas GO improved in 143 patients (84 %). Patients who experienced an improvement of GO after treatment were more likely non-smokers (p=0.009), received glucocorticoids at the time of RAI (p<0.001), had a shorter antithyroid treatment duration (p=0.003), and had a shorter time from onset of GD to RAI treatment (p=0.003).

In conclusion, although RAI treatment of GD is a risk factor for *de novo* occurrence or worsening of GO, it is, in our experience, a reasonably safe treatment if administered timely and with concomitant appropriate methylprednisolone prophylaxis.

References

1. Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf). 2008;69:943–50.
2. Lazarus JH, Bartalena L, Marcocci C, Kahaly GJ, Krassas G, Wiersinga WM. Glucocorticoid administration for Graves' hyperthyroidism treated by radioiodine. A questionnaire survey among members of the European Thyroid Association. J Endocrinol Invest. 2010;33:409–13.
3. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021;185:43-67.
4. Šfiligoj Planjšek D. Potek ščitnične orbitopatije pri bolnikih z Gravesovo boleznijo, zdravljenih z radioaktivnim jodom [PhD Thesis]. Ljubljana: D. Šfiligoj Planjšek; 2019. p. 64-109.
5. Nwatsock JF, Taieb D, Tessonnier L, Mancini J, Dong-A-Zok F, Mundler O. Radioiodine thyroid ablation in Graves' hyperthyroidism: merits and pitfalls. World J Nucl Med 2012;11:7–11.

RADIOIODINE IN ADOLESCENTS

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Introduction

In adolescents with Graves' disease (GD), treatment usually starts with antithyroid drugs. If this treatment is not effective, they are left with only two options: thyroid surgery or radioactive iodine 131 (I-131). Surgery is not perceived a good option by many adolescents, as it is associated with a risk of complications. Thyroid autonomy (TA), however, which is rare in adolescents, is usually treated with I-131 only.

Treatment goal

The goal of treatment of GD in adolescents with I-131 is to establish hypothyroidism. In addition to ensuring permanent hypothyroidism, ablation is also useful for preventing the growth of possible thyroid carcinoma (1). The goal of treatment of TA with I-131 is to establish euthyroidism. In this disease, hypothyroidism occurs later, usually in a few percent of patients annually.

Treatment dose

The efficacy of I-131 therapy is dose related. It also depends on the iodine supply in a certain area. Therefore, various successful doses have been reported. In Japan, for example, a dose of 300 µCi of I-131/g of thyroid tissue provided fairly reliable ablation of thyroid tissue (1). When the dose was too low (several mCi), retreatment was needed (2). In the USA, the reported I-131 doses in children and adolescents have ranged from 100 to 250 µCi/g of thyroid tissue (3). After administering a dose of 150–200 µCi/g of tissue, the long term cure rates of hyperthyroidism were 90% or greater (3). On the other hand, with the I-131 dose of 220 µCi/g of thyroid tissue, a successful treatment rate of 65.6% was reported (4). An I-131 dose close to 250 µCi/g of thyroid tissue had a higher likelihood of achieving hypothyroidism (5). With the median dose of 13 mCi (range 3.6 to 29.8 mCi) 91% of 117 juvenile patients from Japan developed overt hypothyroidism, 2% subclinical hypothyroidism, 5% euthyroidism, and 2% subclinical hyperthyroidism (6). Ultrasound measurement of thyroid volume three months after treatment with I-131 is clinically useful for predicting hypothyroidism. Around 90% of adolescents whose thyroid volume decreased by 50% three months after I-131 treatment became hypothyroid within one year (1).

Treatment safety

No increased risk of adverse events was reported in young GD patients under the age of 20 years who had been treated with I-131 between 1953 and 1973 (2). At the time of treatment with I-131, their ages ranged between 3 years, 7 months and 19 years, 9 months. A follow-up was performed in 107 patients after 26.1 years, and in 98 of them also after 36.2 years. No patient developed thyroid cancer or leukemia. Pregnancies were not associated with higher frequency of complications such as congenital anomalies or spontaneous abortions (2). The follow-up time of 117 juvenile patients aged 10 to 18 years who had been treated with the median dose 13 mCi I-131 ranged between 4 and 226 months (6). New thyroid nodules were detected in 9 patients after 4 to 17 years. These patients received lower doses of I-131 and had larger residual

thyroid volumes than those without nodules. None had thyroid or other malignancies (6). Treating young people with I-131 is safe.

Our experience

Between March 2013 and January 2022, we treated 56 adolescents (46 girls and 10 boys) aged between 14 and 20 with I-131. Among them, 41 had GD and 15 TA. Patients with GD were significantly older than patients with TA (18.5±1.5 and 17.5±1.5 years, respectively, p=0.024). Before I-131, all GD patients were treated with antithyroid drugs for 30 (1–84) months (median, range). No patient with TA was treated with antithyroid drugs before I-131. Thyroid volume in GD patients was significantly larger than the volume of thyroid autonomous tissue in TA patients (median, range, 24.4 (6.5–75) and 7.7 (0.7–24.6) mL, respectively, p<0.001). GD patients were treated with significantly lower dose of I-131 than TA patients (median, range, 724 (500–950) and 902 (572–950) MBq, respectively, p=0.0001). First dose of I-131 was successful in 92.7% of GD patients. Three patients needed the second dose of I-131. Time to the onset of hypothyroidism was in GD patients 2 (1–11) months (median, range). As for TA, hypothyroidism after I-131 occurred in 46.7% of patients after 3 (1–24) months (median, range).

Conclusions

Treatment with radioiodine is a simple, effective and safe treatment option for adolescents with GD and TA.

References

1. Nakatake N, Fukata S, Tajiri J. Prediction of post-treatment hypothyroidism using changes in thyroid volume after radioactive iodine therapy in adolescent patients with Graves' disease. Int J Pediatr Endocrinol. 2011;2011(1):14.
2. Read CH Jr, Tansey MJ, Menda Y. A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. J Clin Endocrinol Metab. 2004;89(9):4229–33.
3. Rivkees SA, Sklar C, Freemarks M. The management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab. 1998;83(11):3767–76.
4. Namwongprom S, Dejkhamron P, Unachak K. Success rate of radioactive iodine treatment for children and adolescent with hyperthyroidism. J Endocrinol Invest. 2021;44(3):541–5.
5. Kaplowitz PB, Jiang J, Vaidyanthan P. Radioactive iodine therapy for pediatric Graves' disease: a single-center experience over a 10-year period. J Pediatr Endocrinol Metab. 2020;33(3);383–9.
6. Mizokami T, Hamada K, Maruta T Higashi K, Tajiri J. Long-term outcomes of radioiodine therapy for juvenile Graves' disease with emphasis on subsequently detected thyroid nodules: a single institution experience from Japan. Endocr Pract. 2020;26(7):729–37.

QUALITY OF LIFE IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES USING ADVANCED HYBRID CLOSED LOOP INSULIN DELIVERY

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Background

Type 1 diabetes (T1D) is one of the most common chronic conditions in children and adolescents all over the world, and the incidence of T1D is increasing by approximately 3.4 % per year in Europe. The goal in the management of T1D is to maintain blood glucose levels as close to normal as possible with the aim of avoiding or delaying disease-related micro- and macrovascular complications. Major guidelines suggest glycated hemoglobin (A1C) below 7 % (53 mmol/mol), but not all patients can achieve this goal. The use of technology in the management of T1D is increasing, and we can

start with a continuous glucose monitor followed by an insulin pump. In the last decade, the two are combined into an automated closed-loop insulin delivery system. There is increasing evidence that the use of advanced hybrid closed loop (AHCL) systems can improve glycemic control irrespective of baseline A1C, with fewer hypoglycemic events. Most of the studies using AHCL show stable glycemic control overnight. This is also important for families since fear of undetected hypoglycemia and hyperglycemia can be the biggest during sleep. Recent data also confirm the ability of the AHCL insulin delivery systems to safely achieve a significant overall improvement in glucose control in T1D.

Methods

24 young people with T1D (14 female) aged 10 to 18 years participated. Data collection before and at the end of AHCL (a period of 4 months) use were analyzed. Qualitative data were obtained with modeled interviews of four focus groups before and at the end of the period. Clinical data were collected from electronic medical records.

Results

The use of AHCL significantly improved the quality of life in terms of decreased fear of hypoglycemia ($p<0.001$), decrease in diabetes-related emotional distress ($p<0.001$), and increased well-being ($p=0.003$). The mean A1C decreased from 8.55± 1.34 % (69.9 mmol/mol) to 7.73± 0.42 % (61.0 mmol/mol) ($p=0.002$) at the end of the study. Mean TIR was 68.22 % (± 13.89) before and 78.26 (± 6.29) % ($p<0.001$) at the end of the study.

Conclusion

The use of AHCL significantly improved the quality of life and metabolic control in children and adolescents with T1DM.

References

1. Patterson CC, Harjutsalo V, Rosenbauer J, et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. Diabetologia. 2019;62(3):408–17.
2. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med. 2014;371:1972–1982.
3. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. Diabetes Care. 2019;42(8):1593–1603.
4. Martin CT, Criego AB, Carlson AL, Bergenstal RM. Advanced technology in the management of diabetes: which comes first-continuous glucose monitor or insulin pump? Curr Diab Rep. 2019;19(8):50.
5. Dovc K, Piona C, Mutlu GY, et al. Faster Compared With Standard Insulin Aspart During Day-and-Night Full Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial. Diabetes Care. 2020;43(1):29-36.
6. Tauschmann M, Thabit H, Leelarathna L, et al. Factors Associated With Glycemic Control During Free-Living Overnight Closed-Loop Insulin Delivery in Children and Adults With Type 1 Diabetes. J Diabetes Sci Technol. 2015;9(6):1346-47.
7. Strandberg RB, Graue M, Wentzel-Larsen,T, et al. The relationships among fear of hypoglycaemia, diabetes-related quality of life and psychological well-being in Norwegian adults with Type 1 diabetes. Diabetes Res Clin Pract. 2017;124:11–19.
8. Hood KK, Laffel LM, Danne T, et al. Lived Experience of Advanced Hybrid Closed–Loop Versus Hybrid Closed–Loop: Patient–Reported Outcomes and Perspectives. Diabetes Technol Ther. 2021;23(12):857-61.
9. Abraham MB, Bock M, Smith GJ, et al. Effect of a Hybrid Closed-Loop System on Glycemic and Psychosocial Outcomes in Children and Adolescents With Type 1 Diabetes. JAMA Pediatr. 2021;175(12):1227-35

MODERN TECHNOLOGIES IN THE TREATMENT OF DIABETES AND PHYSICAL ACTIVITY

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- Regular physical activity is recommended for all individuals with diabetes, as the health-related benefits of being physically active are well established.
- Physical activity has long been proposed as a major hurdle for glucose-responsive insulin therapy as there are numerous factors affecting glucose homeostasis.
- Various clinical guidelines and strategies exist, incorporating recommendations based on current insulin delivery and glucose monitoring modality, that assist maintaining precise glucose control during and after physical activity.

Regular physical activity is recommended for individuals with diabetes, performed as often as possible since the health-related benefits of being physically active are well established (1, 2). Data from the Swedish pediatric diabetes quality registry has also indicated a positive impact of physical activity on glycemic control, regardless of age and gender (3), and its association with improved quality of life (4). More recently, higher amounts

of physical activity were associated with improvements in time in range without significantly increasing the risk for hypoglycemia (5). On the other hand, physical activity is overall associated with an increased risk of glycemic excursions and hypoglycemia, particularly during the physical activity and the night following it (6–8). Consequently are individuals with type 1 diabetes reportedly less active than recommended; less than 20% manage to do aerobic exercise more than two times per week, and about 60% do not engage in structured exercise at all (9). Additionally, an accomplishment of optimal glucose control is complicated by the variability in insulin requirements from one day or night to another and might be difficult to overcome with conventional therapeutic tools (2).

Modern technologies for diabetes care, including continuous subcutaneous insulin infusion (insulin pump), continuous glucose monitoring (CGM) devices, either real–time (rtCGM) that is continuously displaying glucose concentration in the interstitial fluid or intermittently scanned CGM (isCGM), which is a variety displaying glucose values only on demand, have re-shaped the management of diabetes. These devices are enabling many individuals with type 1 diabetes to optimize their glycemic control, improve quality of life, and reduce the burden of type 1 diabetes and there has been reported a global increase in uptake into everyday clinical practice (10–13). Glucose-responsive insulin therapy, such as sensor augment pump, predictive low glucose suspend and automated insulin delivery (AID) might further facilitate the situation and reduce some of the challenges during and after physical activity in type 1 diabetes.

Physical activity has long been proposed as a major hurdle for glucose and studies are now looking into how these systems are performing. Exercise duration, modality, relative and absolute intensity, and fitness capacity all affect glucose homeostasis in people living with type 1 diabetes. Previous studies have demonstrated that the use of predictive low glucose insulin-suspend (PLGS) function could reduce the risk of hypoglycaemia after physical activity and can reduce the risk of nocturnal hypoglycaemia (14). These benefits were, however, achieved at the expense of mildly elevated glucose levels or increased time in moderate hyperglycemia without an increased risk for severe rebound hyperglycemia or diabetic ketoacidosis after the PLGS.

AID combines rtCGM with a modern insulin pump and a sophisticated computer algorithm, which directs insulin (single-hormone) or insulin and glucagon (dual-hormone or bihormonal system) delivery in response to sensor glucose data. The autonomous graduated modulation of insulin (and glucagon) delivery below and above the amount preset in a glucose-responsive manner differentiates AID from conventional insulin pump therapy with or without low-glucose suspend or suspend before low feature (15, 16). AID is now a part of regular clinical reality for many individuals living with type 1 diabetes and its performance during and after physical activity has been extensively evaluated, especially in a controlled environment. AID has been challenged with different exercise protocols of different durations and intensities, using faster insulin formulation, glucagon, in heterogeneous age groups, with additional devices to detect physical activity, such as activity and heart rate monitoring, and adding glucagon to prevent hypoglycemia. These studies have demonstrated reduced frequency and the overall proportion of time spent in hypoglycemia during and after physical activity, including nocturnal hypoglycemia, and generally improved time in range with AID (17–21). There are less published data regarding physical activity in unsupervised or less-supervised settings and future research is needed (22–24).

Several strategies for insulin adjustments and additional carbohydrate consumption regarding physical activity have been suggested and these recommendations should be individualized and tailored based on above-mentioned factors and treatment modalities (25–30). Due to differences in modalities and duration of physical activity, activity-related hormonal responses, different gender and age responses to physical activity, a personalized glucose management plan should be made. This plan should include advice on glucose monitoring, exercise timing, carbohydrate intake, insulin dose modification and avoiding injecting insulin at sites involved in the muscular activity (31). Most common aerobic activities lasting more than 30 minutes are likely to require a reduction in insulin dose during exercise and up to 90 minutes before (32). In addition to this, the risk of nocturnal hypoglycemia is increased following afternoon exercise. For insulin pump users, a combination of pump suspension, or a temporary decrease in basal insulin infusion rate (e.g. 50%) implemented at least 90 minutes

before starting exercise to give a reduced basal effect can be advised. A temporary basal reduction of approximately 20% at bedtime for 6 hours helps reduce the risk of nocturnal hypoglycemia. Some differences in AID strategies for physical activity include the importance of pump suspension if disconnecting during physical activity, fewer grams of uncovered carbohydrates before physical activity (taken close to activity onset to avoid a rise in automatically initiated insulin delivery) and continuing the exercise (temporal) target for several hours after activity or potentially overnight to avoid hypoglycemia (33).

In conclusion, it is vital that most individuals with type 1 diabetes are regularly engaged in physical activity. Current data underscore the synergistic effect of advanced diabetes technologies used concomitantly that should be more readily available to individuals with type 1 diabetes for further improvement of diabetes–related clinical outcomes. Further research is needed to evaluate various physical activity settings and the impact of different intensities, durations and modalities of physical activity using available technologies, especially under less supervised conditions.

References

1. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5(5):377–90.
2. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2018;19:205–26.
3. Beraki Å, Magnuson A, Särnblad S, Åman J, Samuelsson U. Increase in physical activity is associated with lower HbA1c levels in children and adolescents with type 1 diabetes: Results from a cross-sectional study based on the Swedish pediatric diabetes quality registry (SWEDIABKIDS). Diabetes Res Clin Pract. 2014;105(1):119–25.
4. Anderson BJ, Laffel LM, Domenger C, Danne T, Phillip M, Mazza C, et al. Factors associated with diabetes-specific health-related quality of life in youth with type 1 diabetes: The global teens study. Diabetes Care. 2017;40(8):1002–9.
5. Gal JJ, Li Z, Willi SM, Riddell MC. Association between high levels of physical activity and improved glucose control on active days in youth with type 1 diabetes. Pediatr Diabetes [Internet]. 2022 Jul 23 [cited 2022 Aug 28]; Available from: https://pubmed.ncbi.nlm.nih.gov/35822348/
6. Tsalikian E, Mauras N, Beck RW, Tamborlane W V, Janz KF, Chase HP, et al. Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus. J Pediatr. 2005;147(4):528–34.
7. Wilson DM, Calhoun PM, Maahs DM, Chase HP, Messer L, Buckingham BA, et al. Factors Associated with Nocturnal Hypoglycemia in At-Risk Adolescents and Young Adults with Type 1 Diabetes. Diabetes Technol Ther. 2015;17(6):385–91.
8. Metcalf KM, Singhvi A, Tsalikian E, Tansey MJ, Zimmerman MB, Esliger DW, et al. Effects of moderate-to-vigorous intensity physical activity on overnight and next-day hypoglycemia in active adolescents with type 1 diabetes. Diabetes Care. 2014;37(5):1272–8.
9. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: A cross-sectional multicenter study of 18,028 patients. Diabetes Care. 2015;38(8):1536–43.
10. Van Den Boom L, Karges B, Auzanneau M, Rami-Merhar B, Lilienthal E, Von Sengbusch S, et al. Temporal trends and contemporary use of insulin pump therapy and glucose

monitoring among children, adolescents, and adults with type 1 diabetes between 1995 and 2017. Diabetes Care. 2019;42(11):2050–6.

11. Addala A, Auzanneau M, Miller K, Maier W, Foster N, Kapellen T, et al. A decade of disparities in diabetes technology use and HBA1c in pediatric type 1 diabetes: A transatlantic comparison. Diabetes Care. 2021;44(1):133–40.

12. Deshmukh H, Wilmot EG, Gregory R, Barnes D, Narendran P, Saunders S, et al. Effect of flash glucose monitoring on glycemic control, hypoglycemia, diabetes-related distress, and resource utilization in the association of british clinical diabetologists (Abcd) nationwide audit. Diabetes Care. 2020;43(9):2153–60.

13. Charleer S, Mathieu C, Nobels F, De Block C, Radermecker RP, Hermans MP, et al. Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: A real-world study. J Clin Endocrinol Metab. 2018;103(3):1224–32.

14. Abraham MB, Davey R, O'Grady MJ, Ly TT, Paramalingam N, Fournier PA, et al. Effectiveness of a Predictive Algorithm in the Prevention of Exercise-Induced Hypoglycemia in Type 1 Diabetes. Diabetes Technol Ther. 2016;18(9):543–50.

15. Thabit H, Hovorka R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia. 2016;59(9):1795–805.

16. Tauschmann M, Hovorka R. Technology in the management of type 1 diabetes mellitus — current status and future prospects. Nat Rev Endocrinol [Internet]. 2018 Jun 26 [cited 2018 Jul 6];1. Available from: http://www.nature.com/articles/s41574-018-0044-y

17. Dovc K, Piona C, Mutlu GY, Bratina N, Bizjan BJ, Lepej D, et al. Faster Compared with Standard Insulin Aspart during Day-And-Night Fully Closed-Loop Insulin Therapy in Type 1 Diabetes: A Double-Blind Randomized Crossover Trial. Diabetes Care. 2020;43(1):29–36.

18. Dovc K, Macedoni M, Bratina N, Lepej D, Nimri R, Atlas E, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomised controlled crossover trial. Diabetologia. 2017;60(11):2157–67.

19. Elleri D, Allen JM, Kumareswaran K, Leelarathna L, Nodale M, Caldwell K, et al. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: Randomized clinical trial. Diabetes Care. 2013;36(4):838–44.

20. Jayawardene DC, McAuley SA, Horsburgh JC, Gerche A La, Jenkins AJ, Ward GM, et al. Closed-Loop Insulin Delivery for Adults with Type 1 Diabetes Undertaking High-Intensity Interval Exercise Versus Moderate-Intensity Exercise: A Randomized, Crossover Study. Diabetes Technol Ther. 2017;19(6):340–8.

21. Castle JR, El Youssef J, Wilson LM, Reddy R, Resalat N, Branigan D, et al. Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors. Diabetes Care. 2018;41(7):1471–7.

22. Ekhlaspour L, Forlenza GP, Chernavvsky D, Maahs DM, Wadwa RP, Deboer MD, et al. Closed loop control in adolescents and children during winter sports: Use of the Tandem Control-IQ AP system. Pediatr Diabetes [Internet]. 2019 May 23 [cited 2019 Sep 11];20(6):759–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31099946

23. Breton MD, Cherñavvsky DR, Forlenza GP, DeBoer MD, Robic J, Wadwa RP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: The artificial pancreas ski study. Diabetes Care. 2017;40(12):1644–50.

24. Petruzelkova L, Soupal J, Plasova V, Jiranova P, Neuman V, Plachy L, et al. Excellent Glycemic Control Maintained by Open-Source Hybrid Closed-Loop AndroidAPS during and after Sustained Physical Activity. Diabetes Technol Ther. 2018;20(11):744–50.

25. Thabit H, Leelarathna L. Basal insulin delivery reduction for exercise in type 1 diabetes: finding the sweet spot. Diabetologia. 2016;59(8):1628–31.

26. McAuley SA, Horsburgh JC, Ward GM, La Gerche A, Gooley JL, Jenkins AJ, et al. Insulin pump basal adjustment for exercise in type 1 diabetes: a randomised crossover study. Diabetologia. 2016;59(8):1636–44.

27. Diabetes Research in Children Network (DirecNet) Study Group, Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, Janz KF, Ruedy KJ, Wilson D, Xing D WS. Prevention of Hypoglycemia During Exercise in Children With Type 1 Diabetes by Suspending Basal Insulin. Diabetes Care. 2006;29(10):2200–4. Available from: http://care.diabetesjournals.org/cgi/doi/10.2337/dc06-0495

28. Pivovarov JA, Taplin CE, Riddell MC. Current perspectives on physical activity and exercise for youth with diabetes. Pediatr Diabetes. 2015;16(4):242–55.

29. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC. The Effects of Basal Insulin Suspension at the Start of Exercise on Blood Glucose Levels During Continuous Versus Circuit-Based Exercise in Individuals with Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion. Diabetes Technol Ther. 2017;19(6):370–8.

30. Campbell MD, Kime N, McKenna J. Exercise and physical activity in patients with type 1 diabetes. Lancet Diabetes Endocrinol. 2017;5(7):493.

31. Moser O, Riddell MC, Eckstein ML, Adolfsson P, Rabasa-Lhoret R, van den Boom L, et al. Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes: position statement of the European Association for the Study of Diabetes (EASD) and of the International Society f. Pediatr Diabetes. 2020;21(8):1375–93.

32. Zaharieva DP, McGaugh S, Pooni R, Vienneau T, Ly T, Riddell MC. Improved open-loop glucose control with basal insulin reduction 90 minutes before aerobic exercise in patients with type 1 diabetes on continuous subcutaneous insulin infusion. In: Diabetes Care. 2019. p. 824–31.

33. Zaharieva DP, Messer LH, Paldus B, O'Neal DN, Maahs DM, Riddell MC. Glucose control during physical activity and exercise using closed loop technology in type 1 diabetes. Can J Diabetes [Internet]. 2020; Available from: https: //doi.org/10.1016/j.jcjd.2020.06.003

MODERN TECHNOLOGIES DURING PREGNANCY

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Introduction

Pregnancy is a challenging life period, characterized by dynamic changes of insulin sensitivity and glucose tolerance and demands the achievement of tight glycemic control (1). Recently, continuous glucose monitoring (CGM) systems with and without insulin pump therapy are revolutionizing diabetes care (2). In particular, new algorithm-controlled insulin delivery systems based on real-time CGM have changed the clinical landscape by providing new therapeutic targets, as well as an increase in the proportion of people with type 1 diabetes safely achieving these goals (3). However, the value of these systems in pregnant women with type 1 diabetes is still not well characterized. In addition, there is a lack of data on target glucose range, derived from the CGM systems, in pregnant women with type 2 diabetes or gestational diabetes (4).

Continuous glucose monitoring during pregnancy

Continuous glucose monitoring systems can be broadly divided into two types:

1. systems for continuous measurement of glucose in the intercellular space (RT-CGM: "real-time continuous glucose monitoring");
2. systems for intermittent glucose monitoring (IS-CGM: "intermittent system for continuous glucose monitoring" or "flash glucose monitoring").

According to international guidelines, both are recommended in pregnancy as an adjunct and not as a substitute for capillary blood glucose measurement (4).

The recent randomized multicenter study CONCEPTT showed that the use of RT-CGM for capillary blood glucose measurement during pregnancy in type 1 diabetes slightly lowers HbA1c (-0.19%) without an increased risk of hypoglycemia, while reducing the risk of macrosomia of the fetus, neonatal hypoglycemia and shortening the duration of hospitalization compared to only capillary blood glucose concentration measurement (5). In a large cohort study, perinatal outcomes did not differ by sensor system type (IS-CGM or RT-CGM), while pregnant women with type 1 diabetes spent less time hypoglycemic when RT-CGM was used (6). International guidelines have outlined the goals for the treatment of type 1 diabetes during pregnancy (2) with more than 70% of the time spent in the target range ("time in range", TIR), i.e. between 3.5 and 7.8 mmol/l; less than 4% of the time spent in the glucose range of less than 3.5 mmol/l ("time below range", TBR) and less than 25% of the time spent in the range above 7.8 mmol/l ("time above range", TAR).

Intriguingly, a recent large cohort study of type 1 diabetes pregnancies from the Joslin diabetes center has pointed out that although CGM use was associated with better glycemic control (reflected by lower HbA1c), it did not translate into a significant improvement of any of the maternal or neonatal outcomes (7). Of note, a detailed analysis of >10.5 million CGM glucose measures from two large multicenter trials has shown that maternal glucose has the central role in the pathogenesis of excessive

infant growth from the early gestation onwards (8). Moreover, it has been demonstrated that normal birth weight was associated with TBR well above the recommended international consensus target of ≤4%, never falling below 8% in women with normal-sized babies (8).

In Slovenia, we can prescribe RT-CGM sensor systems at the expense of the Health Insurance Institute to pregnant women with type 1 diabetes, while IS-CGM can be prescribed also to pregnant women with type 2 diabetes or gestational diabetes, if they are treated with insulin.

Insulin pump therapy

Insulin pump therapy in women with type 1 diabetes was not conclusively associated with better perinatal outcomes in meta-analyses, but was associated with greater treatment satisfaction and dietary freedom (9). In the CONCEPTT study (5), the effect of CGM was the same regardless of the way insulin was administrated (continuous delivery of glucose in the subcutaneous tissue or multiple daily insulin injections). Some newer systems, where CGM is combined with the continuous delivery of glucose by the help of advanced mathematical computer algorithms, the so-called "closed-loop system", have enabled pregnant women with type 1 diabetes to survive a higher percentage of time in the target glucose range between 3.5 and 7.8 mmol/l (10) or a lower percentage of time in the hypoglycemic range (11). We are still waiting for the results of a randomized controlled study in pregnant women with type 1 diabetes using the Minimed 780G system that includes an advanced hybrid closed loop algorithm, already in clinical use in Slovenia.

Gestational diabetes and continuous glucose monitoring

Gestational diabetes is characterized by the increased glycaemia compared to normal pregnancy, but usually not reaching glucose concentrations typical for pregnancies in women with preexistent diabetes (12). Sensor systems have not yet been tested in large randomized clinical trials in type

2 diabetes or in gestational diabetes. The guidelines therefore point out that in these cases it is not yet clear what the glycemic targets are when using the sensor system, nor whether the use of sensors improves glycemic or perinatal outcomes (4). However, the hypothesis is that CGM devices may be more user friendly to women with GDM compared to capillary blood glucose measurements, may help in improving lifestyle and in gaining less gestational weight (13).

References

1. García-Patterson A, Gich I, Amini SB, Catalano PM, de Leiva A, Corcoy R. Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus: three changes of direction. Diabetologia. 2010;53(3):446-51.

2. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603.

3. Silva JD, Lepore G, Battelino T, Arrieta A, Castañeda J, Grossman B, et al. Real-World Performance of the MiniMed™ 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther. 2022;24(2):113-9.

4. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021;44(Supplement 1):S200-S210.

5. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-59.

6. Kristensen K, Ögge LE, Sengpiel V, Kjölhede K, Dotevall A, Elfvin A, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes: an observational cohort study of 186 pregnancies. Diabetologia. 2019;62(7):1143-53.

7. Wang Z, James-Todd TM, Isganaitis E, O'Connell J, Helman S, Wyckoff JA, et al. Associations of insulin pump and continuous glucose monitoring use with pregnancy-related outcomes in women with type 1 diabetes. Diabetes Research and Clinical Practice. 2022;187:109854.

8. Scott EM, Murphy HR, Kristensen KH, Feig DS, Kjölhede K, Englund-Ögge L, et al. Continuous Glucose Monitoring Metrics and Birth Weight: Informing Management of Type 1 Diabetes Throughout Pregnancy. Diabetes Care. 2022;45(8):1724-34.

9. Lawton J, Kirkham J, Rankin D, White DA, Elliott J, Jaap A, et al. Who gains clinical benefit from using insulin pump therapy? A qualitative study of the perceptions and views of health professionals involved in the Relative Effectiveness of Pumps over MDI and Structured Education (REPOSE) trial. Diabetic Medicine. 2016;33(2):243-51.

10. Stewart ZA, Wilinska ME, Hartnell S, Temple RC, Rayman G, Stanley KP, et al. Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes. N Engl J Med. 2016;375(7):644-54.

11. Stewart ZA, Wilinska ME, Hartnell S, O'Neil LK, Rayman G, Scott EM, et al. Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type

1 Diabetes: A Randomized Controlled Crossover Trial. Diabetes Care. 2018;41(7):1391-9.

12. Nigam A, Sharma S, Varun N, Munjal Y, Prakash A. Comparative analysis of 2-week glycaemic profile of healthy versus mild gestational diabetic pregnant women using flash glucose monitoring system: an observational study. BJOG. 2019;126(S4):27-33.

13. Huhn EA, Linder T, Eppel D, Weißhaupt K, Klapp C, Schellong K, et al. Effectiveness of real-time continuous glucose monitoring to improve glycaemic control and pregnancy outcome in patients with gestational diabetes mellitus: a study protocol for a randomised controlled trial. BMJ Open. 2020;10(11):e040498.

THE ROLE OF GLP-1 IN WOMEN'S REPRODUCTIVE HEALTH

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There is much research-supported evidence about the connection between energy balance and fertility. On one end of the calorie consumption spectrum, chronic energy deficiency has been connected with amenorrhea and infertility (1, 2). On the other end, studies have continuously proven a link between obesity and anovulation, subfertility, infertility and a higher miscarriage rate (3, 4, 5). By some studies, weight loss alone improves the chances of a successful IVF treatment and of successful pregnancy (6, 7, 8, 9, 10).

It is speculated that the amount of energy available to the body impacts fertility and inhibits reproductive capacity during poor nutrition conditions (11). Hormones of the gut (glucagon-like peptide-1 (GLP-1), insulin, ghrelin, obestatin, insulin, peptide YY, glucose-dependent insulinotropic peptide, oxyntomodulin and cholecystokinin) and the adipose tissue (leptin, adiponectin, resistin, omentin, chemerin) control this phenomenon. All of the above-mentioned hormones have been found to be involved in the regulation of human reproduction (12).

GLP-1 is an incretin hormone produced by post-translational processing of proglucagon in enteroendocrine L-cells (13). Its most important role is to regulate insulin secretion, which enables adequate maintenance of postprandial glucose levels (13, 14). It is secreted as one of the gut hormones within minutes after food intake (15, 16). It further stimulates insulin production and improves insulin sensitivity, increases pancreatic β-cell proliferation and protects them from apoptosis. It inhibits glucagon secretion and gastric emptying and suppresses food intake (13, 17–20), which has been shown to be beneficial in weight reduction. GLP-1 binds to the GLP-1 receptor (GLP-1R), which is a member of the G protein-coupled receptor (GPCR) family (21). GLP-1R has also been detected in the lung, stomach, hypothalamus, heart, intestine, ovary and endometrium (22).

Recently, the GLP-1's role as a modulatory molecule in fertility is becoming increasingly apparent (12, 23, 24). GLP-1 receptors (GLP-1R) are distributed throughout the reproductive system, and the effects of GLP-1 are seen at the level of reproduction in both preclinical models and some clinical trials (25) thus suggesting, GLP-1 plays a role in the interaction between the reproductive and metabolic systems (23). Preclinical results suggest that GLP-1 predominantly has a stimulatory effect on the hypothalamic-pituitary axis (26, 27, 28, 29). It was also suggested that GLP-1 and GLP-1 agonists (GLP-1A) have anti-inflammatory and antifibrotic effects on various reproductive tissues, such as the ovaries, endometrium, and testes, which are altered in obesity, diabetes, and polycystic ovary syndrome (PCOS) (23).

GLP-1 modulates the activity of hypothalamic GnRH neurons (26, 27, 28, 29). Further investigations in preclinical models have shown that GLP-1 acts through the modulation of presynaptic excitatory γ -aminobutyric acid (GABA)-ergic inputs and via kisspeptin-1 neurons (29) in the hypothalamus. These are neurons that are essential for fertility (30), as they are key regulators of the pulsatile release of GnRH from GnRH neurons (31). GLP-1 induces an increase in serum LH concentration in the most functional studies (26, 27, 28). GLP-1 related increase in GnRH is being applied as a principal mechanism to stimulate LH secretion from the pituitary. Importantly, the hypothalamic expression of GLP-1R in animal

models varied in a time- and tissue-specific manner through the oestrous cycles. The highest expression level of GLP-1R mRNA in the hypothalamus (27) and the plasma concentrations of GLP-1 were detected during the pro-oestrous phase. The hypothalamic GLP-1 content and plasma LH were also responding to the nutritional status (26).

GLP-1 also has an effect on the ovaries. In addition to the GLP-1 receptors expressed in the ovary (25), GLP-1 has also been demonstrated in follicular fluid (32). Based on pre-clinical and clinical irradiation studies, GLP-1 is most likely to affect steroidogenesis, gametogenesis and gonadal morphology. Most clinical studies show the impact of GLP-1 RAs on hyperandrogenism with reduction of androgens and increase of SHBG in PCOS patients (23).

Studies on the effect of GLP-1 on the menstrual cycle in PCOS patients are also important in determining the impact of GLP-1 on women's reproductive health. Elkind-Hirsch et al. looked at the effect of GLP-1A on menstrual frequency in anovulatory women with PCOS in three randomised groups treated with exenatide, metformin or a combination of the two (33). They found improved ovulation rates in all groups, and the combination treatment led to the best results, with the establishment of ovulation in 86%. Body weight decreased in all groups, and weight reduction was also associated with improved menstrual cycle.

Recent studies on the GLP-1RA's plausible therapeutic role in human infertility treatment showed the positive impact of GLP-1RA on weight loss and improved fertility rate (6, 34). Liu et al. observed the effects of 24 weeks of GLP-1RA (Exenatide) treatment on the spontaneous pregnancy rate in obese or overweight women with PCOS. After 24 weeks of treatment, they observed significant weight loss, central adiposity reduction and an improvement in insulin resistance (IR), menstrual cycle and a decrease in inflammatory markers (34). Our research team conducted a study in which we observed liraglutide's influence on IVF outcomes in infertile, obese, women with PCOS. A 12-week preconception treatment with low-dose liraglutide in combination with metformin was superior to metformin alone in increasing IVF pregnancy rates and the cumulative pregnancy rate including also spontaneous pregnancies after IVF. Suggested mechanisms for the improved pregnancy rate were attributed to weight-loss mechanisms,

improvement of insulin resistance, and the possible effect of GLP-1 on the hypothalamic-pituitary-ovarian axis (6, 34).

In addition, the possible effect of liraglutide on the endometrium was also proposed relating to significantly better implantation rate in the group that was given the combination of metformin and liraglutide (6). We performed the endometrial transcriptomic study to investigate the effect of weight loss with liraglutide on the expression of genes in the human endometrium in obesity and PCOS. We found that endometrial gene expression changed during the implantation window after the weight loss with liraglutide. The most important expressed mechanisms of weight loss with liraglutide were at the level of GLP-1R activation, modulation of inflammation, oxidative stress, glucose metabolism and energy consumption according to the functional transcriptomic analysis of the endometrium. These processes could represent potential mechanisms for optimizing the endometrial environment for implantation and embryo development to successful pregnancy (35).

The distribution of GLP-1R in the reproductive system and the described actions of GLP-1 in preclinical and clinical studies suggest that GLP-1 may be an influential signaling link between the reproductive and metabolic systems. GLP-1A has the potential for novel therapeutic strategies in the treatment of infertility associated with obesity, diabetes and PCOS.

References

1. Vale B, Brito S, Paulos L, Moleiro P. Menstruation disorders in adolescents with eating disorders-target body mass index percentiles for their resolution. Einstein (Sao Paulo). 2014;12(2):175-180.
2. Roberts RE, Farahani L, Webber L, Jayasena C. Current understanding of hypothalamic amenorrhoea. Ther Adv Endocrinol Metab. 2020;11:2042018820945854.
3. Talmor A, Dunphy B. Female obesity and infertility. Best Pract Res Clin Obstet Gynaecol. 2015;29(4):498-506.
4. Bolúmar F, Olsen J, Rebagliato M, Sáez-Lloret I, Bisanti L. Body mass index and delayed conception: a European Multicenter Study on Infertility and Subfecundity. Am J Epidemiol. 2000;151(11):1072-1079.
5. Diamanti-Kandarakis E, Bergiele A. The influence of obesity on hyperandrogenism and infertility in the female. Obes Rev. 2001;2(4):231-238.
6. Šalamun V, Jensterle M, Janež A, Vrtačnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. Eur J Endocrinol. 2018;179(1):1-11.
7. Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. Clin Obes. 2014;4(2):61-68.
8. Moran L, Tsagareli V, Norman R, Noakes M. Diet and IVF pilot study: short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. Aust N Z J Obstet Gynaecol. 2011;51(5):455-459.
9. Espinós JJ, Polo A, Sánchez-Hernández J, et al. Weight decrease improves live birth rates in obese women undergoing IVF: a pilot study. Reprod Biomed Online. 2017;35(4):417-424.
10. Palomba S, Falbo A, Valli B, et al. Physical activity before IVF and ICSI cycles in infertile obese women: an observational cohort study. Reprod Biomed Online. 2014;29(1):72-79.
11. Kennedy GC & Mitra J. Body weight and food intake as initiating factors for puberty in the rat. J Physiol. 1963;166(2):408-418.
12. Comninos AN, Jayasena CN, Dhillo WS. The relationship between gut and adipose hormones, and reproduction. Hum Reprod Update. 2014;20(2):153-174.
13. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87(4):1409-1439.
14. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-165.

15. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nat Rev Endocrinol. 2009;5(5):262-269.

16. Hayes MR, Kanoski SE, Alhadeff AL, Grill HJ. Comparative effects of the long-acting GLP-1 receptor ligands, liraglutide and exendin-4, on food intake and body weight suppression in rats. Obesity (Silver Spring). 2011;19(7):1342-1349.

17. Huang Y, Wilkinson GF, Willars GB. Role of the signal peptide in the synthesis and processing of the glucagon-like peptide-1 receptor. Br J Pharmacol. 2010;159(1):237-251.

18. Li Y, Tweedie D, Mattson MP, Holloway HW, Greig NH. Enhancing the GLP-1 receptor signaling pathway leads to proliferation and neuroprotection in human neuroblastoma cells. J Neurochem. 2010;113(6):1621-1631.

19. Montrose-Rafizadeh C, Yang H, Wang Y, Roth J, Montrose MH, Adams LG. Novel signal transduction and peptide specificity of glucagon-like peptide receptor in 3T3-L1 adipocytes. J Cell Physiol. 1997;172(3):275-283.

20. Quoyer J, Longuet C, Broca C, et al. GLP-1 mediates antiapoptotic effect by phosphorylating Bad through a beta-arrestin 1-mediated ERK1/2 activation in pancreatic beta-cells. J Biol Chem. 2010;285(3):1989-2002.

21. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes Obes Metab. 2018;20 Suppl 1:5-21.

22. Pyke C, Heller RS, Kirk RK, et al. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. Endocrinology. 2014;155(4):1280-1290.

23. Jensterle M, Janež A, Fliers E, DeVries JH, Vrtačnik-Bokal E, Siegelaar SE. The role of glucagon-like peptide-1 in reproduction: from physiology to therapeutic perspective. Hum Reprod Update. 2019;25(4):504-517.

24. Lamos EM, Malek R, Davis SN. GLP-1 receptor agonists in the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2017;10(4):401-408.

25. Nishiyama Y, Hasegawa T, Fujita S, et al. Incretins modulate progesterone biosynthesis by regulating bone morphogenetic protein activity in rat granulosa cells. J Steroid Biochem Mol Biol. 2018;178:82-88.

26. Beak SA, Heath MM, Small CJ, et al. Glucagon-like peptide-1 stimulates luteinizing hormone-releasing hormone secretion in a rodent hypothalamic neuronal cell line. J Clin Invest. 1998;101(6):1334-1341.

27. Outeiriño-Iglesias V, Romaní-Pérez M, González-Matías LC, Vigo E, Mallo F. GLP-1 Increases Preovulatory LH Source and the Number of Mature Follicles, As Well As Synchronizing the Onset of Puberty in Female Rats. Endocrinology. 2015;156(11):4226-4237.

28. Farkas I, Vastagh C, Farkas E, et al. Glucagon-Like Peptide-1 Excites Firing and Increases GABAergic Miniature Postsynaptic Currents (mPSCs) in Gonadotropin-Releasing Hormone (GnRH) Neurons of the Male Mice via Activation of Nitric Oxide (NO) and Suppression of Endocannabinoid Signaling Pathways. Front Cell Neurosci. 2016;10:214.

29. Heppner KM, Baquero AF, Bennett CM, et al. GLP-1R Signaling Directly Activates Arcuate Nucleus Kisspeptin Action in Brain Slices but Does not Rescue Luteinizing Hormone Inhibition in Ovariectomized Mice During Negative Energy Balance. eNeuro. 2017;4(1):ENEURO.0198-16.2016. Published 2017 Jan 20. doi:10.1523/ENEURO.0198-16.2016

30. Gianetti E, Seminara S. Kisspeptin and KISS1R: a critical pathway in the reproductive system. Reproduction. 2008;136(3):295-301.

31. Han SY, McLennan T, Czieselsky K, Herbison AE. Selective optogenetic activation of arcuate kisspeptin neurons generates pulsatile luteinizing hormone secretion. Proc Natl Acad Sci U S A. 2015;112(42):13109-13114.

32. Bou Nemer L, Shi H, Carr BR, Word RA, Bukulmez O. Effect of Body Weight on Metabolic Hormones and Fatty Acid Metabolism in Follicular Fluid of Women Undergoing In Vitro Fertilization: A Pilot Study. Reprod Sci. 2019;26(3):404-411.

33. Elkind-Hirsch K, Marrioneaux O, Bhushan M, Vernor D, Bhushan R. Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;93(7):2670-2678.

34. Liu X, Zhang Y, Zheng SY, et al. Efficacy of exenatide on weight loss, metabolic parameters and pregnancy in overweight/obese polycystic ovary syndrome. Clin Endocrinol (Oxf). 2017;87(6):767-774.

35. Šalamun V. Transkriptom celic kumulusa in endometrija pri neplodnih bolnicah z debelostjo in s sindromom policističnih jajčnikov zdravljenih z metforminom in liraglutidom [online]. 2021. [Cited 2022 Sep 2]. Available from: https://repozitorij.uni-lj.si/IzpisGradiva.php?lang=slv&id=132787

THE ROLE OF GLP-1 (AGONISTS) IN MALE REPRODUCTIVE HEALTH

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Introduction

The reproductive system and energy metabolism are closely interconnected processes in human biology. For a human to reproduce the energy homeostasis needs to be adequately balanced. Prolonged scarcity or energy surplus can disrupt the human reproductive system through complex signalling pathways which are yet to be fully understood. Due to extreme energy abundance, we are currently living in the obesity epidemic which coincides with the rise of male hypogonadism and infertility (1, 2). Obesity and insulin resistance are major contributors to male hypogonadism, with some studies reporting up to 50 % of obese diabetic men to have low levels of circulating testosterone (3). The extensive research on type 2 diabetes and its treatment gave rise to antidiabetic agents based on the incretin system, particularly, glucagon-like-peptide 1 (GLP-1) agonists, which further defined the role of incretins in glucose homeostasis and energy metabolism. Ensuing studies revealed widespread effects of GLP-1 throughout the human body and were not limited to the pancreas and glucose and energy homeostasis. Of particular interest has been the effect of GLP-1 on the male reproductive system. Prolonged treatment with GLP-1 agonists has improved testosterone levels via weight reduction in obese men with hypogonadism. There has also been demonstrated a direct effect of GLP-1 on male gonads and gametes.

The GLP-1 and the incretin system

The incretin system has been extensively studied in the treatment of type 2 diabetes where the effects of GLP-1 agonists have been proven to be particularly successful in improvement of glucose homeostasis by enhancement of insulin secretion and reduction of caloric intake through appetite regulation and decreasing gut motility thereby achieving significant weight reduction (4). The widespread presence of GLP-1 receptors on multiple human tissues, namely lungs, kidneys, heart, and central nervous system, indicates far greater physiological reach than glucose and energy homeostasis (5). In several different tissues, GLP-1 carries out a protective role in preserving cell mass mainly due to its anti-apoptotic and anti-inflammatory function (5).

Energy metabolism and the male reproductive health

The relationship between energy metabolism and the reproductive system is complex and remains to be fully elucidated. Current evidence points to peripheral adipokine inhibition of gonadotropin-releasing hormone secretion via kisspeptin neurons in the hypothalamus (6). The adipokine formation is most pronounced in obese and insulin-resistant states (7). Consequentially, the downregulation of the hypothalamic-pituitary-gonadal (HPG) axis reduces spermatogenesis and testosterone production (6). Interestingly, the HPG axis is reinstated again when the body weight and insulin resistance are reduced. The extent of weight loss and testosterone level elevation seem to be in a reciprocal relationship (8). The role of GLP-1 through its regulation of appetite and reduction of energy intake has proven to be significant in the coupling of the two physiological processes. A study on obese individuals with functional hypogonadism demonstrated significant increase of circulating testosterone levels through the recovery of the HPG axis when continually treated with GLP-1 agonists (9). However, in healthy individuals such treatment, albeit acute, did not affect luteinizing hormone and testosterone levels (10).

The direct role of GLP-1 on male gonads

The presence of the GLP-1 receptor in male gonads indicates a direct role of GLP-1 in the reproductive system but the role remains to be determined. A study has demonstrated the presence of GLP-1 receptors in rodent and human male Leydig cells, but absent in tumour Leydig cells suggesting a role in cell oncogenesis (11). Recognized for its anti-apoptotic and anti-inflammatory role in other tissues GLP-1 could have a similar role in male gonads (5). The absence of GLP-1 function has led to the decreased size of gonads in GLP-1 receptor knockout mice compared to controls (12). Conversely, treatment with a GLP-1 agonist has led to improve the quallity and motility of sperm as well as improve the inflammatory status of the gonads in hypogonadal obese mice models (13). Finally, the direct effect of GLP-1 on human male gametes has been thoroughly demonstrated by Rago et al. The in vitro treatment of gametes with a GLP-1 agonist, exendin-4, demonstrated the effect on several metabolic processes such as an increase in cholesterol influx and lipid metabolism, an increase in gamete insulin secretion and glucose metabolism as well as an increase in sperm motility (14). These findings are consistent with the intensification of metabolic activity and sperm maturation during the capacitation state, indicating a crucial role of GLP-1 in male fertility. It is worth noticing that, in the same study, reduced GLP-1 receptor expression was observed in sperm samples of patients with oligoastenospermia (14).

Despite mostly favourable outcomes from laboratory studies, a few clinical reports are suggesting the negative effects of GLP-1 agonists on sperm quality. A case report of a 35-year-old man examined for infertility demonstrated no sperm motility after a few months of treatment with a GLP-1 agonist, liraglutide, and a complete improvement after the drug discontinuation (15). Up to July 2022, of 38 415 people that reported adverse side effects when taking liraglutide only 2 had a decreased sperm count (16). So far, no other concerns have been raised despite GLP-1 agonists being one of the most widely prescribed antidiabetic agents worldwide.

References

1. Rolland M, Le Moal J, Wagner V, Royère D, De Mouzon J. Decline in semen concentration and morphology in a sample of 26,609 men close to general population between 1989 and 2005 in France. Hum Reprod. 2013;28(2):462–70.
2. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab. 2004;89(11):5462–8.
3. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010;33(6):1186–92.
4. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021;46:101102.
5. Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, et al. GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Front Endocrinol. 2021;12:721135.
6. Roseweir AK, Millar RP. The role of kisspeptin in the control of gonadotrophin secretion. Hum Reprod Update. 2009;15(2):203–12.
7. Rabe K, Lehrke M, Parhofer KG, Broedl UC. Adipokines and insulin resistance. Mol Med. 2008;14(11-12):741–51.
8. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab. 2011;96(8):2341–53.
9. Jensterle M, Podbregar A, Goricar K, Gregoric N, Janez A. Effects of liraglutide on obesity-associated functional hypogonadism in men. Endocr Connect. 2019;8(3):195–202.
10. Izzi-Engbeaya C, Jones S, Crustna Y, Machenahalli PC, Papadopoulou D, Modi M, et al. Effects of Glucagon-like Peptide-1 on the Reproductive Axis in Healthy Men. J Clin Endocrinol Metab. 2020;105(4):1119–25.
11. Caltabiano R, Condorelli D, Panza S, Boitani C, Musso N, Ježek D, et al. Glucagon-like peptide-1 receptor is expressed in human and rodent testis. Andrology. 2020;8(6):1935-45.
12. MacLusky NJ, Cook S, Scrocchi L, Shin J, Kim J, Vaccarino F, et al. Neuroendocrine function and response to stress in mice with complete disruption of glucagon-like peptide-1 receptor signaling. Endocrinology. 2000;141(2):752–62.
13. Zhang E , Xu F , Liang H , Yan J , Xu H , Li Z , et al. GLP-1 receptor agonist exenatide attenuates the detrimental effects of obesity on inflammatory profile in testis and sperm quality in mice. Am J Reprod Immunol 2015;74(5):457–66 .
14. Rago V, De Rose D, Santoro M, Panza S, Malivindi R, Andò S, et al. Human Sperm Express the Receptor for Glucagon-like Peptide-1 (GLP-1), Which Affects Sperm Function and Metabolism. Endocrinology. 2020;161(4):bqaa031.
15. Fontoura P, Cardoso MC, Erthal-Martins MC, Werneck C, Sartorio C, Ramos CF. The effects of liraglutide on male fertility: a case report. Reprod Biomed Online. 2014;29(5):644–6.
16. Victoza and Sperm count decreased - a phase IV clinical study of FDA data. Mountain View, CA: eHealthMe; 2022 [cited 2022 Sep 8]. Available from: https://www.ehealthme.com/ds/victoza/sperm-count-decreased/

INFERTILITY WORK UP – INTERDISCIPLINARY APPROACH INCLUDING GYNECOLOGIST AND ENDOCRINOLOGIST

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Nowadays, in the absence of relevant medical history or physical findings, a complete systematic infertility workup should be advised after 12 months of conceptual failure in women aged <35 years. In women >35 years, this interval is commonly shortened to 6 months and even less in women aged >40 years.

In the infertility workups, the treatment of 4 areas should be included: the assessment of oocyte quantity and quality; assessment of ovulation, ovulatory disorders, and amenorrhea; assessment of other endocrine disorders, which may compound infertility; and genetic screening and in future maybe expanded carrier screening (ECS).

1. **Assessment of oocyte quantity and quality** using different clinical markers is needed for optimizing ovarian stimulation (OS).

1.1. Clinical biomarkers

1.1.1 **Age** Women are born with a given number of nongrowing follicles (NGFs), and this number is progressively declining with age. However, the NGF decline rate may widely vary among individuals, but around 80% of the variance in the NGF populations is because of age alone. Ovarian surgery, gonadotoxic therapy, and genetic or

idiopathic causes may be associated with an accelerated decline in the number of NGFs, leading to primary ovarian insufficiency (POI). Still, age is by far the most reliable biomarker for the prediction of oocyte quality. Embryo euploidy rates show a consistent continuous decline with age starting from approximately the age of 36 years (1).

1.1.2 **Body mass index** BMI is not independently associated with ovarian reserve. However, BMI does affect response to stimulation because it is inversely associated with the circulating follicle-stimulating hormone (FSH) level after exogenous administration. Women with obesity are at increased risk of an inadequate response leading to ART cancellation. Altered follicular environment, due to lipotoxicity and increased production of reactive oxygen species causes oocyte organelle damage. It is assumed that obesity also negatively affects endometrial receptivity (2).

1.2. Hormonal biomarkers

1.2.1. **Basal FSH** has been one of the first biomarkers for the pretreatment assessment of ovarian function. It is elevated in women with diminished ovarian reserve (DOR) and is not biomarker of oocyte quality.

1.2.2. **Basal estradiol** (E2) alone should not be used as a marker of ovarian reserve. However, it is essential for the correct interpretation of a normal basal FSH value. An elevated serum E2 level in advanced-age patients can lower an otherwise elevated basal FSH level into the normal range, thereby causing a misinterpretation of the test.

1.2.3. **The basal LH** levels are not associated with ovarian reserve and oocyte quality. Low basal LH levels are associated with a suboptimal oocyte yield after trigger with a GnRH agonist, and thus, it may be considered when a freeze-all strategy is planned.

1.2.4. **Antimullerian hormone (AMH)** has undeniably been one of the most important pretreatment biomarkers of the general workup

of patients with infertility. Being produced by the granulosa cells of large preantral and antral follicles, AMH has proven to be an excellent biomarker of ovarian reserve with an excellent ability to predict the extremes of ovarian response. It has low intercycle and intracycle variability and remains same at least up to 12 months. Smoking and the use of combined contraceptives, may suppress the serum AMH levels, and seems to be reversible. AMH is not a biomarker associated with oocyte quality.

1.2.5. **Androgens** testosterone levels may be lower in women with DOR because of the reduction of the number of follicles. It is also known that the androgens decline with age.

On the other hand, serum androgens may be associated with oocyte quality in women with PCOS. Hyperandrogenism alters intrafollicular microenvironment, leading to abnormal folliculogenesis and premature arrest of immature developing oocytes. The most common provocative factors of ovarian hyperandrogenism appear to be obesity and insulin resistance, which occur in 50% of the patients. In this context, obesity up-regulates ovarian androgen production primarily via insulin-resistant hyperinsulinemia and, to some extent, via inflammatory cytokines (3).

1.3. Functional Biomarkers

Antral follicle count (AFC) is one of the best biomarkers of ovarian reserve and response to stimulation with an excellent ability to predict low and excessive response to stimulation. Its low intercycle and intracycle variability makes it, along with AMH, a very reliable biomarker. Regarding, oocyte quality AFC is a weak biomarker (4).

1.4. Genetic Biomarkers

Fragile X mental retardation 1 (FMR1) (>200 CGG repeats) can cause intellectual disability, and premutation (approximately 55–200 repeats) has been associated with POI (5).

2. Assessment of ovulation, ovulatory disorders, and amenorrhea

Ovulation can be detected by transvaginal ultrasonography, urinary LH kits and progesterone level of > 3 ng/mL in the mid-luteal phase. They are classified by the nonfunctioning level in the reproductive axis.

World Health Organization (WHO) type I includes disorders of hypothalamic and pituitary origin. Central nervous system abnormalities and/or pituitary tumors should be excluded.

The most common ovulatory disorders are WHO type II disorders, which refer to oligo-anovulation or PCOS. Classically, there have been 3 sets of criteria for diagnosing PCOS, androgen excess, ovulatory dysfunction, or polycystic ovaries. Owing to the fact that PCOS is a more complex metabolic disorder, associated with various degrees of insulin resistance and metabolic syndrome (commonly associated with hyperandrogenism), general workup may require additional examinations. Disorders that mimic the clinical features of PCOS: thyroid disease, hyperprolactinemia; and non-classic congenital adrenal hyperplasia (NCAH) should be excluded.

World Health Organization type III ovulatory disorders— with or without amenorrhea—are associated with elevated gonadotropin levels. This is often associated with autoimmune alterations (3).

3. Assessment of other endocrine disorders

3.1. Screening for **thyroid disorders** has become a standard, given their potential association with early miscarriage rates.

3.2. **Other hormonal markers** Apart from estrogens and progesterone, the measurement of other steroid hormones should be limited to specific patients' categories. **Androgens** play a role in women with PCOS and may be associated with oocyte quality.

3.3. **Determination of cortisol** and other hormones involved in the steroidogenic pathway is essential in cases of suspicion of specific conditions, such as congenital adrenal hyperplasia (CAH), non-classic NCAH or late-onset CAH which tend to manifest later, with more discrete signs, ranging from premature adrenarche and/or various degrees of masculinization.

In addition, Cushing syndrome, a disorder of cortisol excess, can be confused with PCOS because symptoms of hyperandrogenism, such as hirsutism, and menstrual irregularities are often present (6).

References

1. Franasiak JM, Forman EJ, Hong KH, Werner MD, Upham KM, Treff NR, et al. The nature of aneuploidy with increasing age of the female partner: a review of 15,169 consecutive trophectoderm biopsies evaluated with comprehensive chromosomal screening. Fertil Steril. 2014;101:656–63.e1.
2. Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. Fertil Steril. 2017;107:840–7.
3. Polyzos NP, Ayoubi JM, Pirtea P. General infertility workup in times of high assisted reproductive technology efficacy. Fertil Steril. 2022;118:8-18.
4. van Disseldorp J, Lambalk CB, Kwee J, Looman CW, Eijkemans MJ, Fauser BC, et al. Comparison of inter- and intra-cycle variability of anti- Mullerian hormone and antral follicle counts. Hum Reprod. 2010;25: 221–7.
5. Murray A, Schoemaker MJ, Bennett CE, Ennis S, Macpherson JN, Jones M, et al. Population-based estimates of the prevalence of FMR1 expansion mutations in women with early menopause and primary ovarian insufficiency. Genet Med. 2014;16:19–24.
6. Carmina E, Dewailly D, Escobar-Morreale HF, Kelestimur F, Moran C, Oberfield S, et al. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017;23: 580–99.

EPIDEMIOLOGY OF PANCREATIC CANCER

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Introduction

Cancer epidemiology studies the distribution of cancer in populations and its changes over time. It looks at characteristics of different population groups, not only those who get the disease but also those who do not, to find out how these groups differ. The continuous and systematic collection, storage, and analysis of data on all cancer patients is the basis for controlling this significant public health problem. The population-based cancer registries play a crucial role in this. In this abstract, we present the data on new cancer cases (incidence), mortality, and survival of pancreatic cancer patients in Slovenia, Europe, and globally. In the last part, we also give a short overview of known and possible risk factors for developing pancreatic cancer.

The burden of pancreatic cancer

With almost half a million new cases annually, pancreatic cancer is estimated to be the 12th most common cancer worldwide in 2020; more

than half of the new cases occurred in countries at high or very high levels of human development (1). The geographical differences within Europe are not so pronounced; the highest crude incidence rates in 2020 were noted in Germany, Hungary, and Finland (app. 25/100,000) and the lowest (app. 15/100,000) in Poland, Ireland, and Cyprus (2). In Slovenia, the pancreatic cancer incidence is around 400 (20/100,00) which represents 2.5% of all new cancers. The estimated lifetime risk of being diagnosed with pancreatic cancer is 1% for those born after 2010 in Slovenia. The estimated annual change of crude incidence rate over the latest ten years in Slovenia was 2,7% (3). Along with risk factors, the differences in access to health care can affect the reported rates (4). The incidence of pancreatic cancer is projected to rise in the next two decades by more than 60%, and the rise will be steeper in the currently less developed areas (1). There were an estimated 466,000 deaths from pancreatic cancer in 2020, and because of its very high fatality, pancreatic cancer is the seventh most common cause of death from cancer worldwide (1). Given the overall mortality-to-incidence ratio of 0.98, the geographical patterns and trends for mortality are very similar to those observed for incidence (4). Finally, on the global scale, there was a two-times increase in disability-adjusted life-years due to pancreatic cancer, increasing from 4.4 million in 1990 to 9.1 million in 2017 (5).

Characteristics of patients and their disease

Pancreatic cancer is most frequent in elderly people. The risk of developing pancreatic cancer increases as people age: about 85% are at least 60 years old; pancreatic cancer is unusual in people younger than 45 years (3). Pancreatic cancer affects men and women equally. In Slovenian patients with pancreatic cancer diagnosed between 1997 and 2016, most cases (40%) occurred in the head of the pancreas, in 6%, the disease occurred in the tail of the pancreas, and in 5%, in the body of the pancreas. In 4% of cases, the disease occurred as an overlapping lesion of the pancreas. In 35% of cases of pancreatic cancer, the site was not specified. Around 40% of patients did not have their disease confirmed microscopically. The most common histological type among all microscopically confirmed cases was adenocarcinoma, which occurred in 87% of cases. In 10% of cases, the histological type was not specified. The disease was most commonly diagnosed in the distant stage (55%), one-third of patients were diagnosed with the regional disease (6).

Survival

According to the Concord-3 global research of patients diagnosed with cancer during the 15 years between 2000 and 2014 in 71 countries, pancreatic cancer has the lowest survival of all common cancers, with a five-year survival of less than 7% (7). Early diagnosis is crucial to improve survival outcomes for people with pancreatic cancer; with one-year survival in those diagnosed at an early stage six times higher than one-year survival in those diagnosed at stage four (6, 7). Very important is also the age at diagnosis. A study by Huang et al. et al. comparing survival by stage and patient age in four European countries (Norway, the Netherlands, Belgium, and Slovenia) and the United States shows that the three-year survival of patients with stage I–II who were younger than 60 years at diagnosis was 20-34%, in patients aged 60-69 years 14-25%, and in patients over 70 years 9-13%. In patients with stage III-IV, survival was in the range of 2-5% (under 60 years), 1-2% (60-59 years), and 1% (over 70 years) (8).

Risk factors and prevention possibilities

Without effective screening methods, options for primary prevention of pancreatic cancer are of significant importance. Risk factors such as age, race, and family history cannot be modified. Still, primary prevention by altering modifiable risk factors has the potential to decrease the overall risk of pancreatic cancer and warrants further study. Potentially modifiable risk factors include smoking, obesity, diabetes, diet, and alcohol consumption. The best strategy for risk reduction is lifestyle modification: smoking cessation, maintaining a healthy weight, a diet high in fruits and vegetables, regular physical activity, and avoiding heavy alcohol consumption (4).

Conclusion

Pancreatic cancer is among the deadliest types of cancer. Part of the reason lies in the fact that the stage of most patients at diagnosis is locally advanced or disseminated cancer due to the non-specific symptoms and signs of the disease and the aggressiveness of the disease. All professions involved in the study, monitoring, diagnosis, and treatment of pancreatic cancer can, by working together, contribute to efforts to reduce the number of patients and improve the prognosis of patients with pancreatic cancer.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149:778–89.
2. ECIS - European Cancer Information System, European Union, 2022. [cited 2022 July 25]. Available from: https://ecis.jrc.ec.europa.eu.
3. Zadnik, V, Primic Žakelj M, Lokar K, Jarm K, Ivanuš U, Žagar T. Cancer burden in Slovenia with the time trends analysis. Radiol Oncol. 2017;51:47–55.
4. Wild CP, Weiderpass E, Stewart BW, eds. World cancer report. Cancer research for cancer prevention. Lyon: IARC, 2020. p. 367–74.
5. GBD 2017 Pancreatic Cancer Collaborators. The global, regional, and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol. 2019;4:934–47.
6. Zadnik V, Žagar T, Lokar K, Tomšič S, Konjević Duratović A, Zakotnik B. Trends in population-based cancer survival in Slovenia. Radiol Oncol. 2021;55:42–9.
7. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391:1023–75.
8. Huang L, Jansen L, Balavarca Y, Babaei M, van der Geest L, Lemmens V, et al. Stratified survival of resected and overall pancreatic cancer patients in Europe and the USA in the early twenty-first century: a large, international population-based study. BMC Medicine. 2018;16:125.

PANCREATIC CANCER: RISK FACTORS, RISK ASSESSMENT AND SCREENING OF HIGH-RISK INDIVIDUALS

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Introduction

Pancreatic cancer is one of the cancers with the fastest increasing incidence. It is a leading cause of cancer death worldwide (1). At the same time, survival is still among the lowest. Five years after diagnosis, only a few percent of patients are still alive, which makes it one of the five deadliest cancers (2). The medical profession around the world is currently looking for solutions to this problem and an investment in the research of risk prediction, prevention and early detection of pancreatic cancer is fully encouraged. Given that treatment outcomes are better in localized disease, we expect that personalized screening and diagnosing of asymptomatic, potentially curable pancreatic cancers could improve overall survival.

Risk factors

Ageing of the worldwide populations represents an important factor for the increase in the incidence. Anyway, there are other known non-modifiable and also modifiable risk factors. Both may act either independently or jointly. Many modifiable risk factors such as cigarette smoking, obesity, diabetes and alcohol intake are well known and researched. On the other side, we are aware that there are some families where the clustering of pancreatic

cancer is detected. This may be attributed either to common environmental factors or to an underlying genetic predisposition. The proportion of pancreatic cancers that are due to inherited genetic risk factors has been estimated to be between 21.4–36% (3, 4). Lately, several studies have revealed both, high-penetrance rare variants (*i.e. BRCA2, PALB2, BRCA1, ATM, STK11, CDKN2A, PRSS1, MLH1, MSH2, MSH6 and PMS2*), and also low-penetrance common variants that are associated with an increased risk of pancreatic cancer (5-8). However, the identified genetic variations explain only 20–25% of the heritability (4–5% of all pancreatic cancers) (3). For the 20% of familial pancreatic cancers for which a causative mutation has been identified, knowledge of the precise genetic variation can help guide therapeutic decisions for those who develop pancreatic cancer and prompt early detection screening choices for at-risk relatives.

Pancreatic Cancer Screening

Our ability to detect pancreatic cancer and its precursor lesions is slowly improving. Understanding the underlying risk factors and their interactions will enable prevention efforts, like primary prevention strategies, to reduce exposures and to identify high risk individuals. At the moment, screening of the general population for pancreatic cancer is not recommended, since no screening test has proven to be effective in lowering the incidence and/or mortality. Individuals who are at higher risk of developing pancreatic cancer, on the basis of a family burden of pancreatic cancer or a proven genetic predisposition, could be suitable candidates for selective personalized screening with endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography. The International Cancer of the Pancreas Screening Consortium have agreed that screening should be conducted as part of a clinical trial, or if that is not possible, at a center with experience in pancreatic cancer screening (9). The consensus statements support screening using EUS or MRI (9). EUS-based screening trials in both the USA and Europe have shown that asymptomatic precursor lesions as well as cancers, can be detected at an earlier stage. Yet additional research is needed to prove that early detection screening improves pancreatic cancer outcomes (9, 10).

Conclusion

Pancreatic cancer incidence is increasing. The main causes are ageing of the population, as well as increase in the prevalence of modifiable pancreatic risk factors like obesity, diabetes and cigarette smoking (11). The burden of this disease may be therefore reduced by public health interventions such as smoking cessation, obesity prevention and weight loss. On the other side, the inherited genetic pathogenic variants also play an important role in pancreatic cancer risk. Identifying high-risk individuals and offering them pancreatic cancer screening in a research setting, might provide opportunities for earlier detection. Furthermore, the identification of the genetic changes that underlie pancreatic cancer may provide insight into the etiology of this cancer and the opportunity to implement personalized treatment for cancer patients and screening, early detection and cascade genetic testing for relatives at risk (11).

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A et al. Cancer statistics for the year 2020: An overview. Int J Cancer. 2021;149:778–89.
2. Zadnik, V, Primic Žakelj M, Lokar K, Jarm K, Ivanuš U, Žagar T. Cancer burden in Slovenia with the time trends analysis. Radiol Oncol. 2017;51:47–55.
3. Chen F et al. Analysis of heritability and genetic architecture of pancreatic cancer: a PanC4 study. Cancer Epidemiol. Biomarkers Prev. 2019; 28:1238–1245.
4. Lichtenstein P et al. Environmental and heritable factors in the causation of cancer–analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med. 2000; 343:78–85.
5. Jones S et al. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. Science. 2009; 324: 217
6. Roberts NJ et al. Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov. 2016; 6:166–175.
7. Petersen GM et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. Nat Genet. 2010; 42: 224–228.
8. Wolpin BM et al. Genome-wide association study identifies multiple susceptibility loci for pancreatic cancer. Nat Genet. 2014; 46: 994–1000.
9. Goggins M et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020; 69: 7–17.
10. Canto MI et al. Risk of neoplastic progression in individuals at high risk for pancreatic cancer undergoing long-term surveillance. Gastroenterology. 2018; 155:740–751.
11. Klein AP. Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol. 2021;18(7):493-502.

HOW DO WE TREAT MILD AUTONOMOUS CORTISOL SECRETION (MACS)? – SURGICAL TREATMENT

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Who is the patient with mild autonomous cortisol secretion (MACS)? A patient with an adrenal mass and biochemical evidence of hypercortisolemia but without the classical clinical manifestations of overt Cushing's syndrome. MACS encompasses subclinical Cushing's syndrome (CS), subclinical hypercortisolemia, pre-clinical Cushing's, and subclinical autonomous glucocoricoid hypersecretion. Up to 50% of benign adenomas present some degree of cortisol excess depending on diagnostic criteria applied. Prevalence of MACS is estimated to be 1–2% in general population. The main diagnostic criterion is the result of the 1 mg overnight dexamethasone suppression test. Possible autonomous cortisol secretion is diagnosed if the morning cortisol level is in the range 1.9–5 µg/dL (51–138 nmol/L) (1).

Just under 1% of patients with mild autonomous adrenal cortisol secretion will progress to overt CS in the following years. Comorbidities potentially related to MACS are: glucose intolerance or type 2 diabetes mellitus, dyslipidemia, increased visceral fat and low muscle mass, hypertension, increased left ventricular mass, osteoporosis (2, 3, 4).

Based mostly on retrospective observational studies, MACS is reported to be associated with an increased risk of cardiovascular events, increased

mortality, and increased risk for bone fractures. Adrenalectomy or intensive medical treatment of comorbidities? Should all patients with subclinical Cushing's syndrome undergo unilateral adrenalectomy? In the absence of a prospective randomized study, it is reasonable to consider that younger patients and those who have disorders potentially attributable to excess glucocorticoid secretion and have well documented glucocorticoid secretory autonomy are candidates for adrenalectomy.

If adrenalectomy is performed, perioperative glucocorticoid coverage should be administered because of the risk of adrenal insufficiency, hemodynamic crisis, and death.

Is adrenalectomy effective? Adrenalectomy results in improvement of cardiovascular risk factors, improved blood preassure, and metabolic control in patients with possible autonomous cortisol secretion (5). When compared to conservative management, patients with MACS undergoing adrenalectomy experienced improvement in hypertension (RR 11, 95% CI 4.3–27.8), diabetes mellitus (RR 3.9, 95% CI 1.5–9.9) but not in dyslipidemia or obesity.

Adrenalectomy is the way to improve the bone mineral density. In the study of 32 MACS surgically treated patients and 23 MACS non-surgical patients, surgically treated patients showed 30% reduction in vertebral fractures; in the conservatively treated group, follow-up showed 15 times higher risk of new vertebral fractures (6, 7).

Optimal management of MACS is still a matter of debate. The problems are identification of patients likely to benefit, active approach to screening for comorbidities, discussion of treatment options and lack of evidence-based data.

In conclusion, adrenalectomy as a treatment option for MACS is safe and effective. A surgeon experienced in adrenal surgery who will be able to minimize the risk of complications should be engaged. Adrenalectomy may be done laparoscopically, endoscopically via the posterior approach, or as an open procedure. Laparoscopic adrenalectomy, compared with open adrenalectomy, is associated with less pain, shorter hospitalization time, less blood loss, and faster recovery (8). Furthermore, patient's anxiety and cost of healthcare for extensive follow-up should be considered as important factors. After surgical treatment of MACS, quality of life of these patients improves; however, it remains below that of age and gender controls without MACS for up to 15 years (9).

References

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2016; 175(2): G1–G34.
2. Morelli V, Reimondo G, Giordano R, Della Casa S, Policola C, Palmieri S, et al. Long-term follow-up in adrenal incidentalomas: an Italian multicenter study. J Clin Endocrinol Metab. 2014;99(3):827-34.
3. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014;2(5):396-405.
4. Androulakis II, Kaltsas G, Piaditis G, Grossman AB. The clinical significance of adrenal incidentalomas. Eur J Clin Invest. 2011;41(5):552-60.
5. Morelli V, Frigerio S, Aresta C, Passeri E, Pugliese F, Copetti M, et al. Adrenalectomy Improves Blood Pressure and Metabolic Control in Patients With Possible Autonomous Cortisol Secretion: Results of a RCT. Front Endocrinol (Lausanne). 2022;13:898084. doi: 10.3389/fendo.2022.898084. [cited 2022 Aug 31].
6. Salcuni AS, Morelli V, Eller Vainicher C, Palmieri S, Cairoli E, Spada A, et al. Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism. Eur J Endocrinol. 2016;174(3):261-9.
7. Morelli V, Eller-Vainicher C, Palmieri S, Cairoli E, Salcuni AS, Scillitani A, et al. Prediction of Vertebral Fractures in Patients With Monolateral Adrenal Incidentalomas. J Clin Endocrinol Metab 2016; 101 (7): 2768–75.
8. Elfenbein DM, Scarborough JE, Speicher PJ, Scheri RP. Comparison of laparoscopic versus open adrenalectomy: results from American College of Surgeons-National Surgery Quality Improvement Project. J Surg Res. 2013;184(1):216-20.
9. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab. 2006;91(2):447-53.

MILD HYPERCORTISOLISM – CONSERVATIVE MANAGEMENT

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Mild hypercortisolism (mHC) describes an excessive cortisol secretion in patients without the classical clinical manifestations (especially without catabolic characteristics, e.g., proximal muscle weakness, striae, skin fragility, etc.) of Cushing's syndrome (CS) (1). It is also named "subclinical hypercortisolism" or "subclinical CS" (2). However, the term "subclinical" is misleading, as these patients have a higher prevalence of diabetes mellitus type 2 (DM type 2), hypertension, hyperlipidemia, osteoporosis, cardiovascular events, neuropsychologic disorders, and increased mortality (3). In some patients, mHC may also be completely hidden, meaning they only have biochemical (and no clinical) evidence of hypercortisolism. In this case, the term "hidden hypercortisolism" (HidHyCo) has been proposed (4). The term "mild autonomous cortisol secretion" (MACS) defines the presence of mHC in patients with adrenal incidentalomas (AI) (5). Patients with mHC rarely progress towards CS; therefore, mHC is a distinctive chronic disorder rather than a pre-step of CS (3).

The diagnostic criteria used for defining mHC are inconsistent. Most guidelines agree that the first-line test is a 1 mg overnight dexamethasone suppression test (DST), but the cutoff level of cortisol after the test is still

a matter of debate. Suggested cutoff values are 50 nmol/L (1.8 µg/dL), 51 nmol/L (1.9 µg/dL) and 138 nmol/L (5.0 µg/dL) (6). The European guidelines suggest that cortisol levels between 1.9 and 5.0 µg/dL indicate "possible" autonomous cortisol secretion (7). In the presence of mHC, the ACTH levels above 4.4 pmol/L (20 pg/mL) suggest a pituitary origin (1).

The estimated prevalence of mHC is up to 2% in individuals older than 60 and even higher in patients with uncontrolled hypertension, DM type 2, and osteoporosis (4, 8). It is frequently associated with AI, with high variability in prevalence ranging between 5 and 50% (the high variability results from different criteria for diagnosing this condition) (9). It is even more frequent (about 22–42%) in patients with bilateral AI and with larger adrenal tumors (i.e., above 2.4 cm) (9, 10). Mild hypercortisolism has also been described in patients with pituitary incidentalomas with an estimated prevalence of 5% (11).

Patients with mHC have a higher prevalence of osteoporosis and cardiovascular risk factors (hypertension, DM type 2, dyslipidemia, and obesity). Therefore, they have increased cardiovascular events and mortality rates (3, 12, 13). Some data suggest that the extent of comorbidities in mHC depends not only on the amount of adrenal glucocorticoid (GC) production but also on the peripheral activation of cortisone-to-cortisol by the 11 beta-hydroxysteroid dehydrogenase (11BHSD) enzymes and by the GC receptor (GR) sensitivity (14, 15).

Treatment of mHC can be surgical or conservative. Guidelines from 2016 recommend adrenalectomy in patients with MACS (cortisol after DST >138 nmol/L or 5.0 µg/dL) who have at least two comorbidities potentially related to cortisol excess (e.g., DM type 2, hypertension, obesity, osteoporosis), of which at least one is poorly controlled (7). In patients with bilateral adrenal masses and MACS, 2016 guidelines recommend against bilateral adrenalectomy and suggest unilateral adrenalectomy of the dominant lesion in selected patients (considering age, degree of cortisol excess, general condition, comorbidities, and patient preference) (7). However, the adrenalectomy of the dominant lesion is associated with a high number of relapses of hypercortisolism (16). The surgical treatment (i.e., removal of the pituitary adenoma and/or pituitary surgical exploration) in patients with mHC of pituitary origin has never been investigated (1).

Medical therapy in mHC is required in most patients with bilateral adrenal adenomas, in patients refusing surgery, or in whom surgery is not reasonable or safe (e.g., due to advanced age and the high risk of surgical complications). In rare patients with pituitary mHC, scarce data have been provided on the medical therapy with somatostatin analog pasireotide and dopamine agonist cabergoline (1). In the MACS, data are available for some steroidogenesis inhibitors and glucocorticoid receptor antagonists. Metyrapone successfully restored normal cortisol circadian rhythm in six patients with MACS. They also noted a reduced cardiovascular risk marker IL-6 (17). Metyrapone treatment was also used in a prospective study on seven patients with MACS who received a short-term (a few months) metyrapone course as preoperative therapy. In this study, all patients normalized UFC levels and reduced serum and salivary cortisol levels (18).

The use of ketoconazole in mHC was reported in a case report of a 48-year-old woman with bilateral macronodular adrenal hyperplasia (BMAH). Ketoconazole therapy caused rapid normalization of cortisol and ACTH that persisted over ten years of treatment, with no adrenal changes in size (19). We have no data on levoketoconazole and osilodrostat in patients with mHC. Nowadays, two glucocorticoid receptor antagonists are available: mifepristone and relacorilant. Mifepristone was first studied in six patients with MACS, who were treated for four weeks. There was a significant reduction in insulin resistance and cardiovascular benefit in two patients (20). These results were confirmed by the second study performed on eight patients who were treated with mifepristone for six months (21). In the same year, another study showed that mifepristone improved cardiometabolic parameters two weeks after treatment initiation in 4 patients with BMAH, who also experienced an amelioration of glycemic control and hypertension as well as weight loss (22). Relacorilant is a selective GR antagonist that does not bind to the progesterone receptor. Presently, a phase III, randomized, double-blind, placebo-controlled study (GRADIENT, NCT04308590) is in progress assessing the efficacy and safety of relacorilant to treat hypercortisolism in patients with cortisol secreting adrenal adenoma or hyperplasia associated with impaired glucose metabolism and uncontrolled systolic hypertension.

When deciding on the type of medical therapy in patients with mHC, we must consider the side effects of steroidogenesis inhibitors. For example, ketoconazole can be a better choice than metyrapone in women to avoid hirsutism, whereas metyrapone is a better choice in men to prevent hypogonadism. We must avoid ketoconazole in patients taking medication that affects CYP3A4 P450 metabolism. If hepatic aminotransferases significantly increase on ketoconazole, we can use metyrapone as a substitute (23).

References

1. Favero V, Cremaschi A, Falchetti A, Gaudio A, Gennari L, Scillitani A, et al. Management and Medical Therapy of Mild Hypercortisolism. Int J Mol Sci. 2021;22(21):11521.
2. Chiodini I. Diagnosis and Treatment of Subclinical Hypercortisolism. J Clin Endocrinol Metab. 2011;96(5):1223–36.
3. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014;2(5):396–405.
4. Giovanelli L, Aresta C, Favero V, Bonomi M, Cangiano B, Eller-Vainicher C, et al. Hidden hypercortisolism: a too frequently neglected clinical condition. J Endocrinol Invest. 2021;44(8):1581–96.
5. Araujo-Castro M, Sampedro Núñez MA, Marazuela M. Autonomous cortisol secretion in adrenal incidentalomas. Endocrine. 2019;64(1):1–13.
6. Chiodini I, Albani A, Ambrogio AG, Campo M, De Martino MC, Marcelli G, et al. Six controversial issues on subclinical Cushing's syndrome. Endocrine. 2017;56(2):262–6.
7. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1–34.

8. Bülow B, Jansson S, Juhlin C, Steen L, Thorén M, Wahrenberg H, et al. Adrenal incidentaloma – follow-up results from a Swedish prospective study. Eur J Endocrinol. 2006;154(3):419–23.
9. Delivanis DA, Athimulam S, Bancos I. Modern Management of Mild Autonomous Cortisol Secretion. Clin Pharmacol Ther. 2019;106(6):1209–21.
10. Vassilatou E, Vryonidou A, Ioannidis D, Paschou SA, Panagou M, Tzavara I. Bilateral adrenal incidentalomas differ from unilateral adrenal incidentalomas in subclinical cortisol hypersecretion but not in potential clinical implications. Eur J Endocrinol. 2014;171(1):37–45.
11. Toini A, Dolci A, Ferrante E, Verrua E, Malchiodi E, Sala E, et al. Screening for ACTH-dependent hypercortisolism in patients affected with pituitary incidentaloma. Eur J Endocrinol. 2015;172(4):363–9.
12. Debono M, Bradburn M, Bull M, Harrison B, Ross RJ, Newell-Price J. Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas. J Clin Endocrinol Metab. 2014;99(12):4462–70.
13. Morelli V, Reimondo G, Giordano R, Della Casa S, Policola C, Palmieri S, et al. Long-term follow-up in adrenal incidentalomas: an Italian multicenter study. J Clin Endocrinol Metab. 2014;99(3):827–34.
14. Morgan SA, Hassan-Smith ZK, Lavery GG. MECHANISMS IN ENDOCRINOLOGY: Tissue-specific activation of cortisol in Cushing's syndrome. Eur J Endocrinol. 2016;175(2):R83-89.
15. Motavalli R, Majidi T, Pourlak T, Abediazar S, Shoja MM, Zununi Vahed S, et al. The clinical significance of the glucocorticoid receptors: Genetics and epigenetics. J Steroid Biochem Mol Biol. 2021;213:105952.
16. Albiger NM, Ceccato F, Zilio M, Barbot M, Occhi G, Rizzati S, et al. An analysis of different therapeutic options in patients with Cushing's syndrome due to bilateral macronodular adrenal hyperplasia: a single-centre experience. Clin Endocrinol (Oxf). 2015;82(6):808–15.
17. Debono M, Harrison RF, Chadarevian R, Gueroult C, Abitbol JL, Newell-Price J. Resetting the Abnormal Circadian Cortisol Rhythm in Adrenal Incidentaloma Patients With Mild Autonomous Cortisol Secretion. J Clin Endocrinol Metab. 2017;102(9):3461–9.
18. Puglisi S, Perotti P, Barbot M, Cosio P, Scaroni C, Stigliano A, et al. PREOPERATIVE TREATMENT WITH METYRAPONE IN PATIENTS WITH CUSHING'S SYNDROME DUE TO ADRENAL ADENOMA. Endocr Connect. 2018; 7(11):1227–1235.
19. Comte-Perret S, Zanchi A, Gomez F. Long-term low-dose ketoconazole treatment in bilateral macronodular adrenal hyperplasia. Endocrinol Diabetes Metab Case Rep. 2014;2014:140083.

20. Debono M, Chadarevian R, Eastell R, Ross RJ, Newell-Price J. Mifepristone reduces insulin resistance in patient volunteers with adrenal incidentalomas that secrete low levels of cortisol: a pilot study. PloS One. 2013;8(4):e60984.

21. Belokovskaya R, Ravikumar A, Arumugam D, Izadmehr S, Goddard GM, Geer EB, et al. MIFEPRISTONE TREATMENT FOR MILD AUTONOMOUS CORTISOL SECRETION DUE TO ADRENAL ADENOMAS: A PILOT STUDY. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2019;25(8):846–53.

22. Cohan P, East HE, Galati SJ, Mercado JU, Lim PJ, Lamerson M, et al. Mifepristone Treatment in Four Cases of Primary Bilateral Macronodular Adrenal Hyperplasia (BMAH). J Clin Endocrinol Metab. 2019;104(12):6279–90.

23. Daniel E, Newell-Price JDC. Therapy of endocrine disease: steroidogenesis enzyme inhibitors in Cushing's syndrome. Eur J Endocrinol. 2015;172(6):R263-280.

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USTNE PREDSTAVITVE
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THE MULTIDISCIPLINARY ADRENAL TUMOR BOARD: FIRST EIGHT YEARS OF EXPERIENCE IN UMC LJUBLJANA

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Introduction

Adrenal tumors are among the most common tumors in humans. In addition to defining hormonal activity, the radiological appearance of the tumor is crucial for the patient. Therefore, we introduced a multidisciplinary endocrinological and radiological adrenal tumor board at the UMC Ljubljana in 2014.

Analysis of the work of the board

In the first eight years, we discussed 786 patients (469 women (59%), average age 61.47 ± 13.74 years) at 196 meetings (average 2.1 per month). There were mostly unilateral tumors (572, 73%), of which 336 were on the left side (59%). The mean tumor size was 36.21 mm±24.88 mm. Most of the growths appeared benign, i.e., adenomas (n = 382, 48%), myelolipomas (n = 79, 10%), hyperplasia (n = 56, 7%) or cysts (n = 25, 3%). There were

39 nodules defined as a pheochromocytoma (5%), 27 as an adrenocortical carcinoma (3%) and 15 as metastases (2%). In 57 cases the change was too small for a precise diagnosis, or it was not visible at all (7%). In 106 cases there was a formation of another or unexplained etiology or a tumor was outside the adrenal gland (13%).

Conclusion

Adrenal tumors are predominately benign. If their nature can be reliably confirmed at the tumor board, additional examinations or surgical treatment can be spared for relatively rare patients with suspicious tumors.

References

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2016;175(2):G1-G34.
2. Savitz A, Fong B, Hochberg A, Rumore G, Chen C, Yun J, et al. Endocrine Tumor Board: Ten Years' Experience of a Multidisciplinary Clinical Working Conference. Perm J. 2020;24:19.140.
3. Chiapponi C, Santos DPD, Hartmann MJM, Schmidt M, Faust M, Wahba R, et al. Adrenal Surgery in the Era of Multidisciplinary Endocrine Tumor Boards. Horm Metab Res. 2022;54(5):294-299.

ANALIZA EKONOMSKEGA BREMENA SLADKORNE BOLEZNI V SLOVENIJI KOT PODLAGA ZA NAČRTOVANJE BODOČIH STROŠKOV SLADKORNE BOLEZNI IN PRESOJO UKREPOV ZA NJENO OBVLADOVANJE

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Uvod

Ekonomsko breme posameznih bolezni zajema njihove neposredne zdravstvene in nezdravstvene stroške, posredne stroške zaradi izgub produktivnosti ter neotipljive stroške (1, 2). Gre za stroške, ki bremenijo vse relevantne deležnike, torej bolnike, njihove družine, zdravstveni sistem, delodajalce itd. Upoštevanje družbenega vidika omogoča ugotavljanje razporeditve ekonomskega bremena med deležnike, načrtovanje bodočih stroškov glede na demografske in druge trende, z identifikacijo različnih učinkov na različne deležnike pa tudi ustreznejše zasnove analiz upravičenosti ukrepov za obvladovanje bolezni. Pregled tujih raziskav o ekonomskem bremenu sladkorne bolezni (SB) kaže na precejšnjo variabilnost ocenjenega bremena, kar je posledica razlik v uporabljeni metodologiji, zajemu zapletov ter naboru upoštevanih stroškov, pri čemer večina rezultatov kaže, da so neposredni stroški SB višji od njenih posrednih stroškov (3, 4).

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Podobne razlike razkrivajo tudi obstoječe raziskave posameznih elementov ekonomskega bremena SB v Sloveniji (5–8).

Namen

V tem članku na podlagi primerjave obstoječih analiz stroškov SB v Sloveniji predlagamo razširjen zajem neposrednih zdravstvenih stroškov SB z vidika plačnika in podajamo oceno tega bremena na podlagi podatkov ta leto 2019.

Metode

Ocena stroškov je pripravljena na podlagi administrativne baze podatkov ZZZS o izdatkih za zdravila in medicinske pripomočke, izdatkih za zunajbolnišnično dejavnost diabetologije, za prejemnike zdravil za zniževanje glukoze v krvi pa tudi o izdatkih v splošni in drugih zunajbolnišničnih specialističnih dejavnostih. Prav tako so na podlagi relevantnih diagnoz upoštevani izdatki za bolnišnične obravnave oseb s SB in njenih akutnih ter kasnih zapletov. Ocenjeni so tako skupni stroški kot njihova struktura, pa tudi spolno-starostni profili izdatkov.

Rezultati

V Sloveniji so leta 2019 neposredni zdravstveni stroški SB znašali 197,7 milijona evrov, od tega 18,3% za zdravila iz skupine A10, 12,3% za zdravila za zdravljenje zapletov, 10,7% za medicinske pripomočke, 26,4% odstotkov za dejavnost splošnih in specialističnih ambulant ter 32,2% za bolnišnično dejavnost.

Razprava in zaključek

Ocenjevanje neposrednih zdravstvenih stroškov SB bi bilo smiselno izvajati letno, kar bi na podlagi spolno-starostnih profilov izdatkov omogočalo načrtovanje bodočih izdatkov za plačnika. Za potrebe celovite presoje ukrepov za obvladovanje SB pa bi bilo nujno razviti tudi metodologijo za zajem neposrednih stroškov ostalih deležnikov, zlasti pacientov, ter predvsem posrednih stroškov, ki jih je do sedaj v omejenem obsegu naslovila zgolj analiza NIJZ (5).

References

1. Larg A, Moss JR. Cost-of-Illness Studies: A Guide to Critical Evaluation. Pharmacoeconomics. 2011;29(8): 653–671.
2. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20(4): 327–337.
3. Seuring T, Archangelidi O, Suhrcke M. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. PharmacoEconomics. 2015;33(8):811–831.
4. Šalehar A. Analiza ukrepov in spodbud za boljše obvladovanje ekonomskega bremena sladkorne bolezni tipa 2 v Sloveniji. Magistrsko delo. 2018; Ljubljana: Ekonomska fakulteta.
5. NIJZ, Ekonomsko breme sladkorne bolezni v Sloveniji 2012. 2014; Ljubljana: NIJZ.
6. Nerat T; Kos M. Breme sladkorne bolezni tipa 2 s stališča plačnika zdravstvenega varstva v Sloveniji. Zdravstveno varstvo. 2012;52(3):162–180.
7. Janša K, Stariha J, Lotrič Dolinar A, Došenović Bonča P. Prikaz bremena srčno-žilnih dogodkov pri sladkornih bolnikih. 2017; Redni strokovni sestanek Združenja endokrinologov Slovenije.
8. Grelewska J, Jakubczyk M, Niewada M, Lipka I, Petrova G, Tcharaktchiev D, et al. The cost of macro- and microvascular diseases in patients with diabetes mellitus in selected Central and Eastern European countries. J Health Policy Outcomes Research. 2019;1:1–18.

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VLOGA ELASTOGRAFIJE PRI OPREDELITVI HIPERTIROTIČNE FAZE HASHIMOTOVEGA TIROIDITISA

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Izhodišča

Hashimotov tiroiditis je najpogostejša avtoimunska bolezen ščitnice, pri kateri so v zgodnjem poteku možna kratkotrajna obdobja hipertiroze. Razlikovanje hipertirotične faze HT (HHT) od bazedovke je težavno, saj se klinični sliki prekrivata, laboratorijsko diagnosticiranje ni vedno zanesljivo, ultrazvočna ocena morfologije žleze pa se ne razlikuje značilno. Elastografija je novejša metoda za oceno elastičnosti tkiva ščitnice, ki nima prepoznane vloge pri opredelitvi HHT. Zato smo želeli ugotoviti, ali elastografija ščitnice pripomore k razlikovanju HHT od bazedovke.

Metode

V prospektivno raziskavo smo med oktobrom 2021 in julijem 2022 vključili 16 bolnikov s HHT (starost, 41,5±13,9 let) in 33 bolnikov z bazedovko (starost, 36,9±10,5 let) pred pričetkom zdravljenja. V kontrolno skupino smo vključili 34 ščitnično zdravih preiskovancev (starost, 49,7±15,3 let). Ultrazvočno smo izmerili elastičnost parenhima ščitnice z metodo elastografije strižnih valov (»shear-wave« elastografija, SWE). Za izračun SWE smo uporabili mediano vrednost desetih meritev nad obema režnjema ščitnice. Za primerjavo skupin preiskovancev smo uporabili test Mann-Whitney. Za izračun uporabne vrednosti metode SWE smo uporabili analizo ROC ter točnost metode SWE izrazili z meritvijo AUC.

Rezultati

Meritev SWE je bila pri HHT 18,2 kPa (9,0–31,3), pri bazedovki 22,3 kPa (4,8–41,1 kPa), pri zdravih preiskovancih pa 13,2 kPa (5,8–35,0). Med HHT in bazedovko nismo ugotovili statistično pomembne razlike v rezultatih SWE ($p=0,332$). Če smo za razlikovanje med HHT in bazedovko določili mejno vrednost 21,7 kPa, je bila občutljivost metode SWE 57,6 %, specifičnost pa 75,0 % (AUC=0,587). Pri bolnikih s HHT je bila vrednost SWE značilno višja kot pri zdravih preiskovancih ($p<0,001$). Če smo za razlikovanje med HHT in kontrolno skupino določili mejno vrednost 16,5 kPa, je bila občutljivost metode SWE 81,3 %, specifičnost pa 73,5% (AUC=0,778). Tudi pri bolnikih z bazedovko je bila vrednost SWE značilno višja kot pri zdravih preiskovancih ($p<0,001$). Če smo za razlikovanje med bazedovko in kontrolno skupino določili mejno vrednost 18,5 kPa, je bila občutljivost metode SWE 63,6 %, specifičnost pa 91,2 % (AUC=0,770).

Zaključek

Z metodo elastografije ščitnice ne moremo zanesljivo razlikovati med HHT in bazedovko, lahko pa razlikujemo HHT in bazedovko od ščitnično zdravih preiskovancev. Za točnejšo opredelitev vloge elastografije bo potrebna vključitev večjega števila preiskovancev.

Konflikt interesov: ni konflikta interesov

FINAL ADULT HEIGHT IN CHILDREN WITH CENTRAL PRECOCIOUS PUBERTY – A RETROSPECTIVE STUDY

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Background

Central precocious puberty (CPP) is a premature activation of the hypothalamic-pituitary-gonadal axis. Important negative consequence is compromised final height (FH) due to premature growth plate fusion. GnRH analogues (GnRHa) act by suppressing the HPG axis and stopping the progression of puberty and prolonging growth period.

Objectives

We aimed to evaluate the effect of the GnRHa on FH and identify factors that predict FH in children with CPP.

Population and Methods

A retrospective study included 93 children (12 boys and 81 girls) with CPP or menarche before 10 years, that reached their FAH (68 with idiopathic (iCPP) and 25 with an identified likely cause of CPP (nCPP)). Clinical characteristics including FH between the two groups were compared. We also compared FH between the children treated with triptorelin depo (n=71) and untreated children (n=22). Finally, to determine predicting factors for FH, a multiple regression analysis including 48 treated girls with iCPP was conducted. Target height (TH) was calculated based on parental heights. Predicted adult height (PAH) was calculated based on bone age, chronological age, height at diagnosis and ethnicity.

Results

Children with iCPP reached higher FH than children with nCPP (p=0.002). Negative FH SDS in both groups indicated children with CPP are smaller compared to the general population. There was no significant difference in FH between the treated and untreated children. However, the study was retrospective and not randomised. Nonetheless, the treated group gained 31.2 cm since diagnosis compared to 23.7 cm in the untreated group. Predicting factors for FH were bone age at diagnosis, BMI SDS at diagnosis, basal LH, age at initiation and cessation of treatment, height at cessation of treatment, TH SDS and PAH SDS. Our model explained 72% of FH variance (R2=0.72).

Conclusion

Children with nCPP reached lower FH compared to iCPP group. From CPP diagnosis, the treated children gained 7.5 cm more than the untreated; yet, the FAH was not different. Factors that influence FAH are numerous, and should be considered at individualized decision-making. The most important factors that can be influenced are timely diagnosis and therapy, height at treatment cessation and prudent selection of children that can benefit from treatment.

References

1. Chen M, Eugster EA. Central Precocious Puberty: Update on Diagnosis and Treatment. Pediatr Drugs. 2015;17(4):273–81.

2. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol. 2016;4(3):265–74.

3. Bereket A. A Critical Appraisal of the Effect of Gonadotropin-Releasing Hormon Analog Treatment on Adult Height of Girls with Central Precocious Puberty. J Clin Res Pediatr Endocrinol. 2017;9(Suppl 2):33–48.

A PATIENT WITH INTRACTABLE RIGHT LEG PAIN AND PERIMALLEOLAR EDEMA

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Background

Endocrine myopathy refers to muscle symptoms such as weakness, myalgia, or flexion contractures, caused by endocrine disorders. Edema can occur in systemic diseases, including endocrinopathies. We present a 42-year-old male with myopathy and edema who has remained without diagnosis and proper treatment for two years despite several examinations.

Case report

A 42-year-old male presented to the emergency unit with intractable chronic pain in the right leg and bilateral perimalleolar edema. An angiologist, neurologist, and orthopedist were unable to resolve his problems. Two years ago, he also started to notice reduced body and facial hair, low libido, and erectile dysfunction. On physical examination the patient was hemodynamically stable, but pale, with reduced facial and body hair, and bilateral perimalleolar edema. Antalgic gait with protective guarding and

partial flexion contracture of the right hip were noted. Initial laboratory tests were notable for increased myoglobin, CK, and liver function tests. Chest X-rays showed accentuated hilar shadows. After confirming panhypopituitarism, we initiated hydrocortisone and levothyroxine, which resolved the edema. Testosterone was added in due course. A pituitary MRI was suspicious for neurosarcoidosis. Enlarged hilar, mediastinal, and mesenteric lymph nodes were visible on CT scans and on PET/CT. An enlarged lymph node was noted in the region of the right obturator muscle. Mild sensory and motor polyneuropathy was diagnosed with EMG. MRI revealed mild bilateral hip osteoarthrosis. Sarcoidosis was pathohistologically confirmed after mediastinoscopy with lymphadenectomy. After introduction of methylprednisolone, there was rapid and significant amelioration of right leg pain.

Conclusions

Clinical manifestations of sarcoidosis are heterogeneous, so diagnostics is challenging. Our patient presented with severe right leg pain, which subsided with methylprednisolone, probably due to shrinkage of the enlarged lymph node in the region of the right obturator muscle. However, since musculoskeletal symptoms might occur in 6–13% of hypoadrenalism cases, panhypopituitarism could have also contributed not only to perimalleolar edema, but also to myalgia. In patients with unexplained general complaints, such as pain and edema, we should always search for accompanying clinical symptoms and signs that might reveal an underlying endocrine or other systemic etiology.

References

1. Hoshino C, Satoh N, Narita M, Kikuchi A, Inoue M. Painful hypoadrenalism. BMJ Case Reports. 2011.
2. Voortman M, Drent M, Baughman RP. Management of neurosarcoidosis: A clinical challenge. Curr Opin Neurol. 2019;32(3):475–483.
3. Bradshaw MJ, Pawate S, Koth LL, Cho TA, Gelfand JM. Neurosarcoidosis: Pathophysiology, Diagnosis, and Treatment. Neurol Neuroimmunol Neuroinflamm. 2021;8(6):e1084.

IZRAŽENOST ŠČITNIČNIH BOLEZNI MED EPIDEMIJO COVID-19

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Izhodišča

SARS-CoV-2, ki povzroča koronavirusno bolezen 19 (COVID-19), vstopa v celice preko receptorja za angiotenzin konvertazo 2. Izraženost tega receptorja je celo večja v ščitnici kot v pljučih, zato bi lahko bila tudi ščitnica tarča SARS-CoV-2. Z raziskavo smo želeli ugotoviti, ali je bila v času epidemije COVID-19 izraženost ščitničnih bolezni drugačna kot pred epidemijo.

Metode

Raziskava je bila retrospektivna in klinična. Primerjali smo izraženost ščitničnih bolezni pri bolnikih, ki so bili prvič v življenju pregledani v Ambulanti za bolezni ščitnice na Kliniki za nuklearno medicino Univerzitetnega kliničnega centra Ljubljana med 1. 4. 2019 in 29. 2. 2020 (pred epidemijo COVID-19) ter med 1. 4. 2020 in 28. 2. 2021 (med epidemijo COVID-19). Primerjali smo izraženost subakutnega tiroiditisa, Hashimotovega tiroiditisa, bazedovke in avtonomnega tkiva v ščitnici. V analizi smo upoštevali koncentracijo tirotropina (TSH), prostega tiroksina (pT4) in prostega trijodtironina (pT3), vrednost razmerja pT4/pT3, pri subakutnem tiroiditisu pa tudi hitrost sedimentacije eritrocitov, pri bazedovki pa še koncentracijo protiteles proti receptorju za TSH. Primerjali smo tudi ultrazvočno izmerjen volumen ščitnice. Za statistično obdelavo smo uporabili Mann-Whitneyev test.

Rezultati

Ugotovili smo, da so imeli bolniki s subakutnim tiroiditisom med epidemijo COVID-19 statistično značilno večji volumen ščitnice kot pred epidemijo (p=0,003). Bolniki s hipotirozo zaradi Hashimotovega tiroiditisa so imeli med epidemijo statistično značilno višjo koncentracijo TSH (p=0,001), višjo koncentracijo pT3 (p=0,005) in nižje razmerje pT4/pT3 (p=0,031) kot bolniki pred epidemijo. Bolniki z bazedovko so imeli med epidemijo statistično značilno višjo koncentracijo pT4 (p=0,007) in pT3 (p=0,028). Ugotovili pa smo tudi, da je bila pri bolnikih z avtonomnim tkivom v ščitnici v obdobju med epidemijo koncentracija TSH značilno nižja (p=0,0003) kot pred epidemijo.

Zaključek

Zaključimo lahko, da sta bili med epidemijo COVID-19 bolj izraženi hipotiroza zaradi Hashimotovega tiroiditisa in hipertiroza zaradi bazedovke in avtonomnega tkiva v ščitnici, kar bi lahko pripisali zakasnjeni obravnavi bolnikov v Ambulanti za bolezni ščitnice. To pa bi lahko bila posledica slabše dostopnosti do zdravstvenih storitev na primarni ravni v opazovanem obdobju.

Reference

1. Naguib R. Potential relationships between COVID-19 and the thyroid gland: an update. J Int Med Res 2022; 50(2):3000605221082898.

EFFECTIVENESS OF TELEMEDICINE CARE REPLACING STANDARD CARE IN GESTATIONAL DIABETES: A RANDOMIZED CONTROLLED TRIAL

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Background

Telemedicine improves glycemic and perinatal outcomes when used as an adjunct to standard in-person care in gestational diabetes (GDM). However, little is known about its effectiveness when used instead of standard in-person care. Therefore, we aimed to compare the outcomes of the telemedicine care and the standard care in women with GDM.

Methods

In a single-centre, parallel, randomized controlled trial, women were randomized to: (1) telemedicine group, sending glucose readings via an application installed on a smartphone and monthly individual videocalls replacing on-site visits or (2) standard care group with routine monthly on-site visits. The primary outcome was the effectiveness of glycemic control. The secondary outcomes were gestational weight gain, perinatal data, including birth weight, gestational age, incidence of the offspring large for gestational age, preterm birth, preeclampsia and caesarean section.

Results

A total of 106 women were randomized to the telemedicine (n=54) and the standard care group (n=52). The telemedicine group demonstrated less postprandial measurements above the glycemic target (10.4% [3.9–17.9] vs. 14.6% [6.5–27.1]; p=0.015), together with lower average postprandial glucose (5.6±0.3 vs. 5.9±0.4; p=0.004). Percentage of caesarean section was lower in the telemedicine group (9 (17.3%) vs. 18 (35.3%); p=0.038), with no other differences in perinatal outcomes detected.

Conclusions

Telemedicine offers an effective alternative of delivering care in women with GDM. Research, focused on optimizing the tele-care delivery, limiting the extent of health professional's involvement with the use of automated decision support tools is needed to achieve optimal prenatal care via telemedicine and at the same time to alleviate the burdened health system.

IMMUNE CHECKPOINT INHIBITOR-ASSOCIATED AUTOIMMUNE DIABETES PRESENTING AS DIABETIC KETOACIDOSIS: A SINGLE-CENTRE CASE SERIES

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Introduction

Immune checkpoint inhibitor (ICI) therapy transformed oncologic care (1). Its use increased due to outstanding efficiency and a significant improvement in patient prognosis (2). The key representatives are monoclonal antibodies targeting programmed cell death protein 1 (pembrolizumab, nivolumab) and its ligand and cytotoxic T lymphocyte-associated protein 4 (ipilimumab) (3). One of their immune-related adverse effects is irreversible pancreatic β-cell failure leading to the so-called ICI-associated autoimmune diabetes (CIADM). Although rare, it usually presents with diabetic ketoacidosis (DKA) (4). We review the clinical characteristics of patients hospitalized in our department for DKA and CIADM to explore possible predictive factors for CIADM.

Presentation of cases

Three patients (2 men, 1 woman; aged 56±15 years; body mass index 31±4 kg/m2) were hospitalized in our clinical department with newly diagnosed CIADM and DKA. Two were treated with pembrolizumab (malignant melanoma), one received ipilimumab and nivolumab (renal cell carcinoma). Before confirmation of diabetes, they received 12.5 doses [4–21] of pembrolizumab; 3 doses of ipilimumab and 6 doses of nivolumab. The median time from the last immunotherapy to the presentation of diabetes was 20 days [7–39]. A personal history of diabetes was negative with normal fasting blood glucose prior to immunotherapy. The 3 patients presented with DKA. At the presentation of DKA, the median HbA1c was 10.6 % [7.8–12.2]; the plasma glucose 31.6 mmol/L [18.9–42.2], the pH 7.18±0.2, HCO3- 9.7±4.6 mmol/L, with an anion gap of –17.6±9.4 mmol/L. 2/3 patients had positive ketones urinalysis. Low levels of C-peptides and negative pancreatic autoantibodies were determined. In one patient, asymptomatic COVID-19 infection was confirmed at the time of presentation of the DKA. Ketoacidosis was treated according to the standard protocol and resolved in all patients. They were discharged with multiple daily subcutaneous insulin injections.

Conclusions

In the three patients, ICI-associated autoimmune diabetes and DKA were confirmed; no other predictive parameters were found. To avoid life-threatening DKA, insulin treatment is suggested after confirmation of diabetes (4). Guidelines for the detection of hyperglycemia must be strictly followed during the use of ICI to diagnose diabetes and begin treatment promptly (3).

References

1. Goldman JW, Mendenhall MA, Rettinger SR. Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management. Oncologist. 2016;21(11):1326-1336.

2. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375-91.

3. The Joint British Diabetes Societies (JBDS) for Inpatient Care Group. The Management of Glycaemic Control in People with Cancer: Guidance for the oncology and diabetes multidisciplinary team. Available at: https://abcd.care/resource/jbds-17-management-glycaemic-control-people-cancerAccessed Sept 2021. Accessed: 21/07/2022.

4. Wu L, Tsang VHM, Sasson SC, Menzies AM, Carlino MS, Brown DA, et al. Unravelling Checkpoint Inhibitor Associated Autoimmune Diabetes: From Bench to Bedside. Front Endocrinol (Lausanne). 2021;12:764138.

STRUKTURIRANI IZOBRAŽEVALNI PROGRAM ZA OSEBE, KI BODO NUDILE LAIČNO PODPORO BOLNIKOM S SLADKORNO BOLEZNIJO IN ARTERIJSKO HIPERTENZIJO NA PRIMARNI ZDRAVSTVENI RAVNI V SLOVENIJI

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Uvod

Za dobro presnovno urejenost bolnika s sladkorno boleznijo (SB) in arterijsko hipertenzijo (AH) je potrebno kontinuirano spremljanje bolnikovega zdravstvenega stanja in pridruženih bolezni, pri čemer sta ključna vseživljenjsko izobraževanje in podpora, ki bosta bolnika opolnomočila, da bo lahko samostojno in optimalno skrbel za svojo bolezen (1–3). Uporaba modela integrirane oskrbe je pokazala, da je v Sloveniji najslabše implementirano prav področje samoobvladovanja bolezni in samopomoči (4). Ena izmed možnih rešitev, kako nadgraditi obstoječi model celostne oskrbe kroničnih bolnikov s SB in AH, je uvedba in ustrezna organizacija laične podpore bolnikom in njihovim oskrbovalcem s pomočjo posebej usposobljenih oseb, ki bodo svoje znanje, izkušnje in podporo prostovoljno prenašali na druge bolnike s SB in AH.

Metode

V Zdravstvenem domu (ZD) Ljubljana in ZD Slovenj Gradec smo pridobili 36 bolnikov s SB in/ali AH, ki so se v manjših skupinah udeležili 15-urnega strukturiranega izobraževanja. 31 posameznikov je uspešno zaključilo program, ki je obsegal 2 skupinski in 2 individualna izobraževanja z edukatorico. Udeleženci so pred in po zaključku edukacije izpolnili vprašalnike o socio-demografskih in kliničnih podatkih, poznavanju SB (5) in AH (6), kakovosti življenja s SB (7) in sprejemljivosti intervencije (8).

Rezultati

Za nudenje laične podpore bolnikom s SB in AH se je usposobilo 10 moških in 21 žensk. Njihova povprečna starost je bila 63,9 ± 8,9 let, za SB so se zdravili 14,3 ± 11,7 let in za AH 7,9 ± 8,1 let. V primerjavi z znanjem ob vstopu v raziskavo se je pomembno povečalo njihovo znanje o SB ($p<0,001$) kot tudi o AH ($p=0,022$). Vpliv na kvaliteto življenja je bil nepomembno boljši ($p=0,146$). Udeleženci so izobraževalni program ocenili kot visoko sprejemljiv v vseh 7 domenah sprejemljivosti. Skupna povprečna ocena na 5-stopenjski lestvici je bila 4,45 ± 0,50.

Zaključki

Protokol izobraževalnega programa za usposabljanje oseb, ki bodo nudile laično podporo bolnikom s SB in AH, se je izkazal za visoko sprejemljivega in učinkovitega, kar nakazuje velik potencial za uspešno implementacijo laične podpore na primarni zdravstveni ravni.

Reference

1. Powers MA, Bardsley JK, Cypress M, Funnell MM, Harms D, Hess-Fischl A, et al. Diabetes Self-management Education and Support in Adults With Type 2 Diabetes: A Consensus Report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. Diabetes Care. 2020;43(7):1636–49.
2. Pongrac Barlovič, Draženka. Slovenske smernice za klinično obravnavo sladkorne bolezni tipa 2. Ljubljana: Diabetološko združenje Slovenije, 2022; 2022.
3. Davis J, Fischl AH, Beck J, Browning L, Carter A, Condon JE, et al. 2022 National Standards for Diabetes Self-Management Education and Support. Diabetes Care. 2022;45(2):484–94.
4. Klemenc-Ketis Z, Stojnić N, Zavrnik Č, Ružić Gorenjec N, Danhieux K, Lukančič MM, et al. Implementation of Integrated Primary Care for Patients with Diabetes and Hypertension: A Case from Slovenia. Int J Integr Care. 2021;21(3):15.
5. Prevolnik Rupel V, Ogorevc M, Poplas-Susič A. PMU99 Knowledge of Disease Among Patients with Type 2 Diabetes and Hypertension in Slovenia. Value Health. 2020 Dec;23:S620.
6. Turk Eva, Palfy M., Prevolnik Rupel V. General knowledge about diabetes in the elderly diabetic population in Slovenia. Zdr Vest. 2012;81:517–25.
7. Carey MP, Jorgensen RS, Weinstock RS, Sprafkin RP, Lantinga LJ, Carnrike CL, et al. Reliability and validity of the appraisal of diabetes scale. J Behav Med. 1991;14(1):43–51.
8. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res. 2017;17(1):88.

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HEALTH RELATED QUALITY OF LIFE IN OLDER PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES

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Background

Diabetes is widely present in older adults and consequently this chronic disease is affecting health and emotional wellbeing of a vast portion of worlds' population. Health related quality of life (HRQOL) is an independent predictor of health outcomes that predicts mortality in patients with diabetes, even more prognostic than some physiological diabetes specific factors. The aim of the present study was to determine differences in Health-related quality of life (HRQOL) and self-rated mental health between older adults of both diabetes types and associations of diabetes control, complications, and comorbidities with HRQOL domains.

Methods

We included type 1 (T1D) and type 2 diabetes (T2D) patients, aged ≥ 60 years (n=56), age- and HbA1c- matched. They completed validated Questionnaires (Short Form-36, The EuroQol-5 Dimensions/Visual Analog Scale, The Hospital Anxiety and Depression Scale, The Problem Areas in Diabetes). The outcomes were compared between diabetes types by independent sample t-test. Univariate linear regression analysis was used to establish disease-related factor's impacts on self-rated health scores.

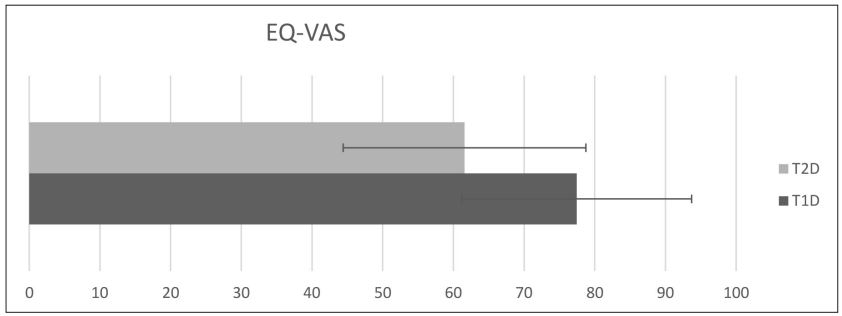
Results

The average age of patients was 68.9 ± 7.8 years, 55% had T2D. General health assessment differed between diabetes types in older T2D and T1D, that reported of better outcomes, while no differences in self-reported diabetes distress, anxiety or depression were proven. Mean EQ-5D VAS score was significantly lower in T2D (61.6 ± 17.2 vs. 77.5 ± 16.2, p=0.002) indicating worse overall impression of self-rated health compared to T1D (Figure 1). Most of the domains of HRQOL were not associated with HbA1c and neither presence of complications. However, multiple regression model suggested that BMI is a predictor of HRQOL.

Conclusion

Older T1D patients rated their general health better compared to their T2D counterparts. Most of the domains od HRQOL were not associated with HbA1c or presence of complications, BMI could be a predictor of some physical health domains. Given the complex nature of interaction of diabetes- related factors with HRQOL, this research argues that HRQOL and glycaemic control are central outcomes in clinical diabetes care but should be evaluated separately.

Figure 1. **EQ-VAS score according to diabetes type.**



Legend: EQ-VAS – EuroQoL-Visual analog scale, T1D Type 1 diabetes patients, T2D Type 2 diabetes patients, values are presented as mean ± SD, *Denotes statistical significance at P < 0.05

References

1. Alonso J, Ferrer M, Gandek B, Ware JE, Aaronson NK, Mosconi P, et al. Health-related quality of life associated with chronic conditions in eight countries: Results from the International Quality of Life Assessment (IQOLA) Project. Qual Life Res. 2004;13:283–98.

2. Anderson BJ, Laffel LM, Domenger C, Danne T, Phillip M, Mazza C, et al. Factors Associated With Diabetes-Specific Health-Related Quality of Life in Youth With Type 1 Diabetes: The Global TEENs Study. Diabetes Care. 2017;40:1002–9.

3. Feng Y, Parkin D, Devlin NJ. Assessing the performance of the EQ-VAS in the NHS PROMs programme. Qual Life Res. 2014;23:977–89.

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SEVERE POSTMENOPAUSAL HYPERANDROGENISM AND A PITUITARY TUMOR: A DIAGNOSTIC CHALLENGE?

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Postmenopausal hyperandrogenism results from absolute or relative androgen excess. It presents with hirsutism, acne, and androgenetic alopecia, in most severe cases with virilisation. We must differentiate between rare tumorous, and common, nontumorous (functional) causes. Diagnosis is based on detailed history and clinical examination, followed by measurement of dehydroepiandrosterone-sulphate and testosterone with additional hormone testing and imaging when necessary (1).

We present a 51-year-old postmenopausal patient with severe, rapidly progressing hyperandrogenism and substantially elevated total testosterone. She was diagnosed with acromegaly due to elevated insulin-like growth factor 1 and pituitary tumour on MRI, despite lacking acromegalic features and appropriate growth hormone suppression after glucose load (2). A second opinion was requested by neurosurgeon. We found a Leydig cell tumour of the right ovary. After bilateral salpingo-oophorectomy, testosterone levels normalised and hyperandrogenism subsided. Since insulin growth

factor 1 also normalised, we concluded that its high levels were caused by the stimulatory effect of testosterone on the somatotropic axis (3). The pituitary tumour was recognized as macroprolactinoma. Prolactin normalised with a dopaminergic agonist. A follow-up MRI is scheduled to confirm the tumour shrinkage.

If hyperandrogenism is clinically suspected in a postmenopausal female, a diagnostic algorithm should be followed. In addition to serum androgen value, the timing of onset, progression and severity of hyperandrogenism are also very important (1). When there is a combination of aetiologies for hyperandrogenism, the diagnosis can be challenging – as it was in the presented case. Only testing of all pituitary-peripheral axes enables optimal management of patients with a pituitary tumour (2).

References

1. Markopoulos MC, Kassi E, Alexandraki KI, et al. MANAGEMENT OF ENDOCRINE DISEASE: Hyperandrogenism after menopause. European Journal of Endocrinology. 2015;172(2): R79–R91

2. Freda PU, Beckers AM, Katznelson L, et al. Pituitary Incidentaloma: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2011;96(4): 894–904.

3. Birzniece V. Hepatic actions of androgens in the regulation of metabolism. Curr Opin Endocrinol Diabetes Obes. 2018;25(3): 201–208.

IMPROVEMENT IN GLYCEMIC CONTROL WITH THE USE OF THE ADVANCED HYBRID CLOSED-LOOP MINIMED 780G SYSTEM IN PATIENTS WITH TYPE 1 DIABETES: FIRST EXPERIENCE IN AN OUTPATIENT CLINIC

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Background

Long-term glycemic control can be challenging with long-lasting type 1 diabetes. Advanced technology, the MiniMed 780G system with an advanced hybrid closed-loop (AHCL) algorithm, enables automated delivery of basal and correction bolus insulin, thus overcoming several obstacles to reach optimal glycemic control (1). Our objective was to evaluate the effect of the introduction of the AHCL system on glycemic parameters in eligible middle-aged patients with type 1 diabetes.

Methods

Seventeen patients with type 1 diabetes were included, 53 % were women, the mean age was 48.4 ± 2.9 years, and the mean duration of diabetes was 22.5 ± 3.9 years. The parameters analyzed were glycated hemoglobin (HbA1c), time in range (TIR), time above range (TAR) and time below range (TBR). In addition, associations were established between the use of the SmartGuard function and glycemic parameters.

Results

Before the introduction of the AHCL system, glycemic control was poor (HbA1c 7.7 ± 0.3 %; TIR 58.4 ± 3.3 %). Sixty days after the introduction of the AHCL system, the HbA1c level decreased to 6.8 ± 0.1 % (P=0.001), while TIR increased to 76.2 ± 1.7 % (P=0.03). After the introduction of the AHCL system, the average TAR was 21.2 ± 1.9 % and the TBR 2.5 ± 0.6 %. The patients used the SmartGuard function 83.9 ± 5.9 % of the time. SmartGuard use was associated with improved HbA1c (R=-0.49; P=0.05). HbA1c after the introduction of the AHCL system correlated with TIR (R=-0.63; P=0.01). Most patients evaluated the use of the new AHCL system as easy while providing satisfactory glycemic control results.

Conclusion

The introduction of the new AHCL MiniMed 780G system resulted in a significant improvement in glycemic control in middle-aged patients with type 1 diabetes in our outpatient clinic; the results were similar to those in other studies (2, 3), but the data are limited. Optimal glycemic control was already achieved 60 days after the introduction of the new device. These results are promising and merit longer-term studies to further explore the new AHCL system in the population with type 1 diabetes.

References

1. Ferrito L, Passanisi S, Bonfanti R, Cherubini V, Minuto N, Schiaffini R, et al. Efficacy of advanced hybrid closed loop systems for the management of type 1 diabetes in children. Minerva Pediatr (Torino). 2021;73(6):474-85.
2. Silva JD, Lepore G, Battelino T, Arrieta A, Castaneda J, Grossman B, et al. Real-World Performance of the MiniMed 780G System: First Report of Outcomes from 4120 Users. Diabetes Technol Ther. 2022;24(2):113-9.
3. Beato-Vibora PI, Gallego-Gamero F, Ambrojo-Lopez A, Gil-Poch E, Martin-Romo I, Arroyo-Diez FJ. Rapid Improvement in Time in Range After the Implementation of an Advanced Hybrid Closed-Loop System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2021;23(9):609-15.

FIRST CLINICAL EXPERIENCE OF THE EFFICACY AND SAFETY OF ORAL SEMAGLUTIDE IN POORLY CONTROLLED TYPE 2 DIABETES

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Background and aim

Recently, the first oral glucagon-like receptor agonist (GLP-1RA), oral semaglutide (1), became available in Slovenia, thus allowing the removal of the frequent treatment barrier of injectable therapy (2). Oral semaglutide proved effective in glycaemia control and body mass reduction in randomised controlled trials (3). However, data from everyday clinical practice are missing. Therefore, we explored the efficacy and safety of oral semaglutide in our outpatient clinic in the first patients with poorly controlled type 2 diabetes who received oral semaglutide.

Methods

In this analysis, the first 20 patients with poorly controlled type 2 diabetes (11 men, 9 women) were included in whom oral semaglutide was prescribed in our outpatient clinic. The baseline average HbA1c was 9.4 ± 0.3%. We followed glycated haemoglobin (HbA1c), fasting blood glucose, and body weight after oral semaglutide introduction. Adverse effects were also recorded.

Results

The mean age of the included patients was 59.9 ± 1.5 years, the mean duration of diabetes 8.5 ± 1.4 years, and the mean body mass index was 34.6 ± 1.4 kg/m^2. Seven patients received two antidiabetic medications (metformin + sulphonylurea) while 13 patients received three medications (metformin + sulphonylurea + SGLT-2 or DPP-4 inhibitor) prior to oral semaglutide introduction. Oral semaglutide at doses of 7 mg or 14 mg daily significantly improved glycaemic parameters: HbA1c (-1.2%; $p<0.05$ and -1.6%; $p<0.01$, respectively) and fasting blood glucose values (-17.8% and -20.4%; both $p<0.05$), respectively). Body weight decreased significantly during oral semaglutide treatment at a dose of 14 mg daily (-11.9%; $p<0.05$). Gastrointestinal adverse effects (particularly reduced appetite, nausea, and obstipation) were recorded in half of the patients; they were mainly mild and transient.

Conclusions

Oral semaglutide, the first GLP-1RA available for oral administration, improved glycaemic parameters and decreased body weight in daily clinical practice in our outpatient clinic, even in patients with poorly controlled type 2 diabetes and in addition to substantial previous oral antidiabetic therapy. Therefore, oral semaglutide appears to be an effective and safe treatment option in uncontrolled type 2 diabetic patients.

References

1. Chan M, Dimitriou A, Lam S. Semaglutide: A Novel Oral Glucagon-Like Peptide Receptor Agonist for the Treatment of Type 2 Diabetes Mellitus. Cardiol Rev. 2021;29(2):100-8.
2. Byrne J, Willis A, Dunkley A, Fitzpatrick C, Campbell S, Sidhu MS, et al. Individual, healthcare professional and system-level barriers and facilitators to initiation and adherence to injectable therapies for type 2 diabetes: A systematic review and meta-ethnography. Diabet Med. 2022;39(1):e14678.
3. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: The PIONEER programme. Diabetes Obes Metab. 2020;22(8):1263-77.

NIZKE PORODNE MERE V POVEZAVI S CENTRALNO PREZGODNJO PUBERTETO – RETROSPEKTIVNA RAZISKAVA

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Izhodišče

Centralna prezgodnja puberteta (CPP) je prezgodnja aktivacija hipotalamo-hipofizno-gonadne (HHG) osi. Različna bolezenska stanja, predvsem v povezavi z osrednjim živčevjem, lahko pozvročijo CPP, večinoma pa je idiopatska. Dejavniki tveganja za razvoj CPP niso natančno opredeljeni. Nizka porodna teža je povezana z večjim pridobivanjem telesne teže v otroštvu, kar lahko sproži prezgodnjo adrenarho in pubarho, vendar povezava s CPP v literaturi zaenkrat ni opisana

Namen

Želeli smo opredeliti, ali imajo otroci s CPP nižje porodne mere kot splošna populacija in, ali je nizka porodna teža lahko dejavnik tveganja za CPP.

Metode

Retrospektivno smo analizirali klinične podatke 142 otrok s CPP, ki smo jih razdelili na skupino z idiopatsko CPP (iCPP) (n=104) in neidiopatsko CPP (nCPP) (n=38) ter primerjali klinične značilnosti med skupinama z metodami opisne statistike. Prevalenco nizke porodne teže in nizke gestacijske starosti smo primerjali s populacijskimi nacionalnimi podatki s testom za testiranje enakosti deleža.

Rezultati

Otroci z nCPP so imeli značilno nižjo gestacijsko starost od otrok z iCPP (p=0,031). Med otroci s CPP je bil delež nedonošenih 11%. Med iCPP so največji delež predstavljali zmerno nedonošeni (32-36 tednov), med nCPP pa izjemno nedonošeni (<28 tednov). Pod 50. percentilom porodne teže je bilo 70% otrok z iCPP in 62% z nCPP. Pod 50. percentilom porodne dolžine je bilo 53% otrok z iCPP in 73% otrok z nCPP. Razlika med skupinama ni bila statistično značilna. V primerjavi s slovensko populacijo novorojenčkov rojenih leta 2015, so imeli otroci s CPP nižjo porodno težo in porodno dolžino glede na gestacijsko starost. Med nCPP je bil značilno večji delež izjemno nedonošenih. Med CPP je bil večji delež otrok z nizko porodno težo neodvisno od gestacijske starosti: pri iCPP je bila razlika pri nizki (2499–1400g) in pri zelo/izjemno nizki (<1500g) porodni teži, pri nCPP pa le pri zelo/izjemno nizki porodni teži.

Zaključek

Porodna teža in dolžina pri otrocih s CPP sta pomaknjeni k nižjim vrednostim v primerjavi s slovensko populacijo. Izrazita nedonošenost je značilna le za nCPP in je povezana s spremembami OŽ ter tudi etiološko s CPP. Nizka porodna teža je bolj pogosto prisotna pri otrocih s CPPkot v splošni populaciji in lahko predstavlja dejavnik tveganja za njen nastanek.

References

1. Latronico AC, Brito VN, Carel JC. Causes, diagnosis, and treatment of central precocious puberty. Lancet Diabetes Endocrinol. 2016;4(3):265–74.

2. Hernández MI, Mericq V. Impact of being born small for gestational age on onset and progression of puberty. Best Pract Res Clin Endocrinol Metab. 2008;22(3):463–76.

3. Ibáñez L, Potau N, Francois I, de Zegher F. Precocious pubarche, hyperinsulinism, and ovarian hyperandrogenism in girls: relation to reduced fetal growth. J Clin Endocrinol Metab. 1998;83(10):3558-62.

PARATHYROID CARCINOMA: A RARE CAUSE OF HYPERCALCEMIA

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Primary hyperparathyroidism is usually caused by parathyroid adenoma or hyperplasia. Parathyroid carcinoma is a rare cause of hyperparathyroidism, accounting for approx. 0.74% of cases. Features that increase the likelihood of parathyroid carcinoma in patients with primary hyperparathyroidism are larger tumor size, symptomatic disease, marked hypercalcemia and very high serum parathyroid hormone (iPTH) concentrations. Preoperative localization studies do not reliably distinguish carcinoma from adenoma, a definitive diagnosis is made if there is local invasion or lymph node or distant metastases.

Case report

65-year-old asymptomatic patient with diabetes mellitus and arterial hypertension was referred to our outpatient clinic because of accidentally found hypercalcemia, with calcium 2.79 mmol/l (normal range 2.2-2.6 mmol/l), ionized-calcium 1.40 mmol/l (1.12-1.23 mmol/l) and intact parathyroid hormone 194 ng/l (10-65 ng/l). We performed ultrasonography of neck region and subtraction thyroid scan. Investigations did not confirm neck mass. We performed choline PET CT that showed larger cystic mass on the right side of thyroid gland, suspicious for parathyroid carcinoma. Before surgery he did CT scan of neck and thorax, which showed large 4x3x5 cm tumor of parathyroid gland, without distant metastases. The patient was referred to a thoracic surgeon. Histological findings of resected tumor confirmed parathyroid carcinoma, TNM stage was T1N0M0. His serum calcium and iPTH concentrations after surgery were normal (Ca 2.12 mmol/l, iPTH 30 ng/l). There were no other complications of the disease. During 5 years of follow-up, his condition has been stable, there has not been any other endocrine disorder. Genetic testing (for mutation of HRPT2) has not yet been completed.

Conclusions

Primary hyperparathyroidism is often recognized as a result of biochemical screening. Most patients are asymptomatic with mildly elevated serum calcium. Although there is overlap in the clinical in biochemical presentation of benign parathyroid disease and parathyroid cancer, there are some features that increase likelihood of parathyroid cancer, one of them is tumor size. Follow-up is indicated as the recurrence rate is high.

REDEK VZROK ZASTOJA SRCA: PARAGANGLIOM

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Uvod

Feokromocitom in paragangliom sta redka nevroendokrina tumorja, ki izločata kateholamine. Povzročata različne srčno-žilne zaplete, ki so lahko usodni: ventrikularne aritmije, akutni miokardni infarkt, hipertenzivo krizo in kardiogeni šok.

Prikaz primera

51- letni bolnik, ki se je več let zdravil zaradi AH z večtirno terapijo, je bil napoten v endokrinološko ambulanto zaradi suma na sekundarno AH.

V januarju 2022 je doživel zunajbolnišnični srčni zastoj, prvi ritem VF. S preiskavami v času hospitalizacije so izključili kardialne vzroke srčnega zastoja in zaradi zastoja srca nejasnega vzroka vstavili ICD. Zaradi visokih vrednosti krvnega pritiska so postavili sum na sekundarno AH. Določili so kateholamine v 24 urnem urinu 3x. V enem vzorcu je bil mejno povišan normetanefrin (2,48 umol/dan, meja 2,13).

Opravil je CT trebuha, kjer je bila vidna 12 mm velika okrogla sprememba v desni nadledvičnici, ki po radioloških kriterijih ni predstavljala maščobno bogatega adenoma. Ob tem je bila vidna mehkotkivna sprememba pred desnim m. psoas - sum na NET.

Ob 4 tirni antihipertenzivni terapiji je bil krvni pritisk dobro urejen. Napadov tipičnih za feokromocitom ni navajal. V statusu z izjemo prekomerne telesne teže ni bilo posebnosti.

Ambulanto smo 2x določili plazemske metanefrine in normetanefrine, ki so bili negativni.

Opravil je PET CT (F-18 FDG), ki je pokazal nizko metabolno aktivno formacijo pred desnim m. psoas. Glede na karakteristike je sprememba predstavljala NET ali paragangliom.

Priporočen je bil PET/CT z 68Ga-DOTATAT, ki je potrdil paragangliom. Sprememba v desni nadledvičnici ni bila metabolno aktivna.

Ponovno smo določili kateholamine in dopamin v 24 urnem urinu 2x. V enkratnem vzorcu sta bila povišana metanefrin 2,07 (do 1,62) in normetanefrin 7,32 (do 2,13). Povišan je bil tudi kromogranin A: 1094,0 (ref. območje 19,4 - 101,9).

Bolnika smo predstavili na urološkem konziliju, priporočena je laparoskopska odstranitev paraganglioma po ustrezni predoperativni pripravi.

Razprava

S kateholamini povzročena kardiomiopatija je redek, vendar nevaren zaplet feokromocitoma in paraganglioma. Nenadno sproščanje kateholaminov iz tumorja poviša srčni utrip, sistemsko žilno upornost, kontraktilnost miokarda in zmanjša vensko komplianco. Ob preveliki adrenergični stimulaciji pride do hude vazokonstrikcije in koronarnega vazospazma.

Smernice priporočajo slikovno diagnostiko ob sumu na feokromocitom/paragangliom le ob pozitivnih biokemičnih testih. Pri bolniku smo, kljub negativnim biokemičnim testom, ob visokem sumu na endokrini vzrok hipertenzije opravili slikovno diagnostiko, s katero smo potrdili paragangliom in s tem verjeten vzrok srčnega zastoja.

References

1. Lenders JWM, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SKG, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline J Clin Endocrinol Metab. 2014;99(6):1915-42.

2. Santos JRU, Bruna AB, Pacak VK. Catecholamine-Induced Cardiomyopathy in Pheochromocytoma: How to Manage a Rare Complication in a Rare Disease? Horm Metab Res. 2019;51(07):458–469.

EPIDEMIOLOGY OF CENTRAL PRECOCIOUS PUBERTY, PREMATURE ADRENARCHE AND ISOLATED TELARCHE IN SLOVENIA

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Background

Decreasing age at the onset of puberty, but stable age at menarche is observed in recent decades in several populations (1). In line with this observation, a rising incidence of central precocious puberty (CPP) is identified in some countries (2). Precocious adrenarche is in most cases an isolated condition of early rise in adrenal androgens, commonly associated with childhood obesity (3). Precocious telarche sometimes occure as an isolated temporal or persistent condition unrelated to activated hypothalamic-pituitary-gonadal axis.

Objectives

We aimed to define the national incidence and trends of CPP, isolated precocious adrenarche (PA) and isolated persistent precocious telarche (PT).

Population and Methods

In a retrospective study, the data on Slovenian national incidence on CPP, PA and PT was collected from an electronic system at the national referral center for pediatric pubertal disorders, Department of Pediatric Endocrinology, Diabetes and Metabolic diseases of the University Children's Hospital of Ljubljana for the time frame between 2011 and 2021. The population of risk was defined as girls of 7 years of age or younger and boys of 8 years of age or younger that lived in Slovenia in a specific year.

Results

The national incidence of CPP was 12.97/100,000 (23.11/100,000 girls, 4.42/100,000 boys). The incidence in girls was rising from 12.57/100,000 in 2011 up to 34.31/100,000 in 2021. In 83.25% of girls, CPP was idiopathic (iCPP), while in boys, the potential cause of the condition was found in 77% of the cases (non-idiopathic CPP - nCPP). There was no sex difference in the incidence of nCPP. The incidence of PA in girls was 35.33/100,000 and in boys 4.195/100,000 and showed no rising trend. The Incidence of PT in girls was 6.04/100,000 and remained stable during observation period.

Conclusions

It is possible that better CPP recognition due to ameliorated education of primary pediatricians impacted rising numbers of identified children with CPP. However, rising CPP incidence during short observation period could also suggest important contribution of yet unidentified environmental factors in iCPP etiology, particularly in girls. However, these may not have the same effect on PA and PT incidence. Earlier pubertal maturation should be acknowledged as an increasing need for care by the national health system.

References

1. Eckert-Lind C, Busch AS, Petersen JH, Biro FM, Butler G, Bräuner EV, Juul A. Worldwide Secular Trends in Age at Pubertal Onset Assessed by Breast Development Among Girls: A Systematic Review and Meta-analysis. JAMA Pediatr. 2020;174(4):e195881.
2. Bräuner EV, Busch AS, Eckert-Lind C, Koch T, Hickey M, Juul A. Trends in the Incidence of Central Precocious Puberty and Normal Variant Puberty Among Children in Denmark, 1998 to 2017. JAMA Netw Open. 2020;3(10):e2015665.
3. Rosenfield RL. Normal and Premature Adrenarche. Endocr Rev. 2021;42(6):783-814.

ENDOCRINE DYSFUNCTION AFTER IPILIMUMAB AND NIVOLUMAB CANCER IMMUNOTHERAPY: A CASE PRESENTATION

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Introduction

Anticytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) and anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1) immune checkpoint inhibitors (ICI) have significantly improved cancer outcomes (1). However, due to their mechanism of action, immune-related adverse events, most often endocrine dysfunctions (thyroiditis, hypophysitis, adrenal gland disorders, diabetes) can be triggered (2). Combined therapy has shown the highest risk of occurrence of adverse events (3). We present a patient who suffered insufficiency of three endocrine glands after combined immunotherapy with ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1).

Case presentation

A 58-year-old man with a history of several chronic non-communicable diseases and metastatic clear cell renal carcinoma of the right kidney on maintenance chemotherapy with nivolumab was hospitalized after a newly discovered diabetes presented as diabetic ketoacidosis (DKA). In the weeks following his last round of chemotherapy, he noticed general weakness, headaches, and dizziness. Polydipsia, nocturia, and urinary frequency became more evident days before hospitalization. When examined, he was hypotensive and nauseous with episodes of vomiting; laboratory tests showed hyponatremia, hyperkalemia, hyperglycaemia, and metabolic acidosis (low bicarbonate and pH). Ketoacidosis was treated according to the standard protocol and resolved completely. However, the patient tested positive for COVID-19 and received remdesivir, remaining asymptomatic throughout the infection. During hospitalization, hypothyroidism, and adrenal insufficiency (basal cortisol 40 nmol/L and 98 nmol/L 30 minutes after stimulation, respectively) were diagnosed. Substitution treatment with levothyroxine and hydrocortisone was introduced. Hyperglycemia was regulated with multiple daily insulin injections. Higher sodium values found in the urine suggested the concomitant syndrome of inappropriate antidiuretic hormone secretion (SIADH). This, among hypophysitis, hypothyroidism and diabetes, could also be a side effect of nivolumab immunotherapy.

Conclusions

In the case presented, we confirmed multiple endocrinopathies (diabetes, hypothyroidism, and probably secondary adrenal insufficiency due to hypophysitis) as a consequence to ICI oncological immunotherapy treatment. Therefore, in patients who receive this class of immunotherapy, caution is advised for endocrinopathies due to possible life-threatening adverse events (ketoacidosis, adrenal crisis, etc.) and appropriate substitution therapy should be introduced promptly (3).

References

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350-5.
2. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, Tolaney SM. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA Oncol. 2018;4(2):173-82.
3. Ovčariček T. Imunoterapija. Onkologija (Ljubljana). 2018;22(1):18-22.

CLINICAL CHARACTERISTICS OF FIRST SLOVENIAN PATIENTS WITH TYPE 2 DIABETES WHO WERE TREATED WITH ORAL SEMAGLUTIDE: A MULTICENTER STUDY

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Background and aim

GLP-1 receptor agonists (GLP-1RA) are suggested in patients with type 2 diabetes at increased cardiovascular risk or with established atherosclerotic cardiovascular disease (ASCVD) (1, 2). Until recently, GLP-1RA was only available in injectable form, which frequently caused treatment barriers from the patient or medical personnel (3). Oral semaglutide, the first GLP1-RA in oral form, could overcome these barriers (4). The purpose of the present study was to analyse the clinical characteristics of the first patients who received oral semaglutide in Slovenia in four different hospitals.

Methods

The first 45 patients (23 women, 22 men) with type 2 diabetes who were treated with oral semaglutide were analysed. We establish background antidiabetic treatment, the reason for the introduction of oral semaglutide, and their risk of ASCVD. Glycated haemoglobin (HbA1c) and fasting blood glucose were also collected at the start of the study.

Results

The patients were 61.9 ± 1.5 years old, obese (stage 3, mean body mass index 35.8 ± 0.8 kg/m2) with a duration of type 2 diabetes of 9.8 ± 1.6 years. Most patients received a triple combination of metformin, gliclazide, and SGLT-2 inhibitor (45%) or a dual combination of metformin and gliclazide (40%), others received a combination of metformin and SGLT-2 inhibitor (8%) or metformin, gliclazide, and DPP-4 inhibitor (7%) prior to oral semaglutide introduction. In most patients, oral semaglutide was introduced due to poorly controlled glycemia (45%), fear of injections (20%), obesity (22%). 11 patients (24.5%) had known ASCVD; 19 patients (42.2%) had a high risk of ASCVD. The mean HbA1c at the introduction of oral semaglutide was 9.3 ± 0.3% and fasting blood glucose 10.8 ± 0.5 mmol/l.

Conclusion

In a Slovenian cohort of the first 45 patients with type 2 diabetes who received oral semaglutide, the main reasons for its introduction were poorly controlled glycemia, fear of injections, and obesity. Most of the patients had received triple antidiabetic treatment before and were at high cardiovascular risk. Due to the change in the insurance policy in Slovenia, we expect more patients to benefit from oral semaglutide sooner after the diagnosis of type 2 diabetes.

References

1. American Diabetes Association Professional Practice Committee; Boris Draznin, Vanita R Aroda, George Bakris, Gretchen Benson, Florence M Brown, RaShaye Freeman, Jennifer Green, Elbert Huang, Diana Isaacs, Scott Kahan, Jose Leon, Sarah K Lyons, Anne L Peters, Priya Prahalad, Jane E B Reusch, Deborah Young-Hyman. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care, 2022;45(Suppl 1):S125-S143.
2. Draženka Pongrac Barlovič, et al. Slovenske smernice za klinično obravnavo sladkorne bolezni tipa 2, 2022.
3. Kruger DF, LaRue S, Estepa P. Recognition of and steps to mitigate anxiety and fear of pain in injectable diabetes treatment. Diabetes Metab Syndr Obes. 2015;8:49–56.
4. Bucheit JD, Pamulapati LG, Carter N, Malloy K, Dixon D, Sisson EM. Oral Semaglutide: A Review of the First Oral Glucagon-Like Peptide 1 Receptor Agonist. Diabetes Technol Ther. 2020;22(1):10-18.

PROTECTION OF THE VASCULAR SYSTEM THROUGH THE ANTIOXIDANT AND ANTI-INFLAMMATORY ACTION OF THE EMPAGLIFLOZIN-METFORMIN COMBINATION

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Background

Cardiovascular benefits of antihyperglycemic drugs have become one of the key criteria for choosing the type 2 diabetes treatment (1). The empagliflozin-metformin combination improved endothelial function and reduced arterial stiffness, thus proving functional cardiovascular benefit (2). However, the mechanisms behind this finding are not yet fully understood. Therefore, the purpose of our study was to explore the possible antioxidant and anti-inflammatory action of empagliflozin-metformin combination in patients with type 1 diabetes, naive to any antihyperglycemic therapy with cardiovascular protection.

Methods

Forty male patients with type 1 diabetes were randomly assigned to four groups: (1) control (placebo), (2) empagliflozin 25 mg daily, (3) metformin 2000 mg daily, and (4) empagliflozin-metformin combination (25 mg and 2000 mg daily, respectively) in addition to their regular insulin therapy (multiple daily injections or continuous subcutaneous insulin infusion). Their average age was 44.7 ± 2.5 years and the average duration of diabetes was 22.6 ± 3.9 years. Blood samples were collected to determine the parameters of oxidative stress (total antioxidative status (TAS), superoxide dismutase (SOD), glutathione peroxidase (GPx), uric acid, advanced oxidation protein products (AOPP), advanced glycosylation end products ((AGE) and isoprostane), and inflammation parameters (C-reactive protein (CRP) and interleukin-6 (IL-6)) parameters at inclusion and after 3 months of therapy.

Results

The empagliflozin-metformin combination increased antioxidant levels (TAS, SOD and GPx up to 1.1-fold; $P < 0.01$), decreased pro-oxidant levels (AOPP and isoprostanes up to 1.2 times, $P < 0.01$; AGE up to 1.5-fold, $P < 0.01$), and decreased inflammatory parameters (up to 1.5-fold, CRP $P < 0.01$; IL-6 $P < 0.001$). The antioxidant action was associated with an improvement in arterial function in the empagliflozin-metformin combination group.

Conclusions

The empagliflozin-metformin combination had a strong antioxidant and anti-inflammatory action, which was greater compared to individual drugs in patients with type 1 diabetes. In addition, the antioxidant activity of the empagliflozin-metformin combination could at least partially explain the improvement in arterial function. We propose that these results could be extrapolated to patients with type 2 diabetes.

References

1. American Diabetes Association Professional Practice C, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S125-S43.
2. Lunder M, Janic M, Japelj M, Juretic A, Janez A, Sabovic M. Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. Cardiovasc Diabetol. 2018;17(1):153.

DINAMIKA TELESNE TEŽE PRI SLADKORNIH BOLNIKIH, ZDRAVLJENIH Z GLP1-RA (ANALIZA PODATKOV IZ VSAKDANJE KLINIČNE PRAKSE)

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Uvod

Bolniki s sladkorno boleznijo (SB) tipa 2 so pogosto prekomerno prehranjeni ali debeli. V tuji literaturi se tako vse pogosteje uporablja skovanka »diabesity« (1). Zmerna izguba telesne teže ugodno vpliva na urejenost glikemije, zato smernice bolnikom priporočajo izgubo vsaj 5% telesne mase, pri izbiri zdravil za zdravljenje SB pa njihov učinek na telesno težo. Med novejša zdravila z ugodnim učinkom ne telesno težo spadajo tudi agonisti receptorjev GLP1 (GLP1-RA) (2).

Namen, cilji in metode

Da bi pridobili osnovni vpogled v učinek GLP1-RA na telesno težo naših bolnikov, smo v diabetološki ambulanti Bolnišnice Topolšica retrospektivno analizirali podatke o telesni teži pri bolnikih s SB tipa 2 in predpisanim enim od GLP1-RA, ki so v zadnjih 6 mesecih prišli na redni kontrolni pregled. Drugih pomembnih dejavnikov, ki bi lahko vplivali na rezultate, nismo preverjali (urejenost glikemije, sočasna terapija, doslednost jemanja zdravil, frekvenca kontrolnih pregledov ipd.). Analiza je potekala z vgrajenimi osnovnimi statističnimi funkcijami programa Microsoft Excel.

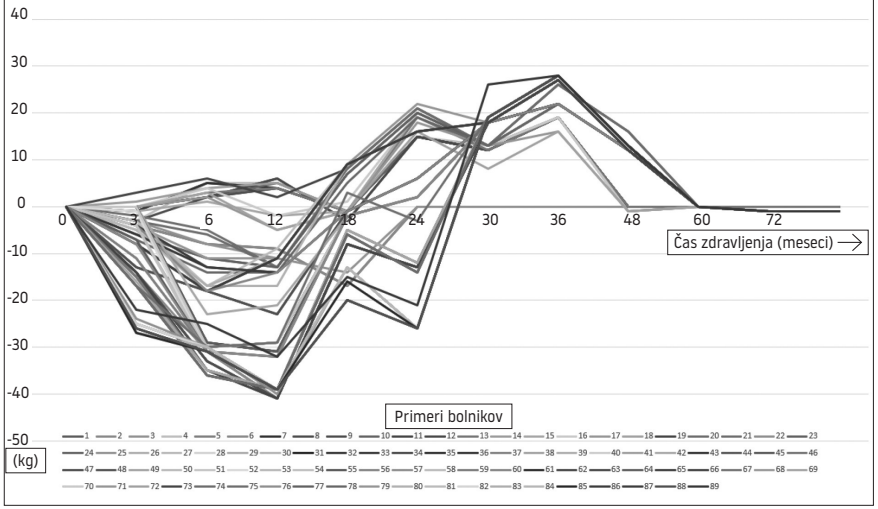
Rezultati

Skupaj smo pregledali podatke za 89 bolnikov, med katerimi je 28 prejemalo

dulagutid, 18 liraglutid (vsi v kombinaciji z inzulinom), 23 semaglutid s.c. in 20 semaglutid p.o.

Dinamiko telesne teže bolnikov skozi čas prikazuje Graf 1.

GRAF 1.
Spremembe izhodiščne telesne teže pri bolnikih s SB tip 2, zdravljenih z GLP1-RA.



Gibanje telesne teže za posamezne GLP1-RA med trajanjem zdravljenja prikazuje Tabela 2.

TABELA 2.
Gibanje telesne teže za posamezne GLP1-RA med trajanjem zdravljenja.

	Trajanje zdravljenja [meseci] →	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**48**
Povprečna sprememba izhodiščne telesne teže za posamezne GLP1-RA [kg]	**Dulaglutid**	0	-0,6	-1	+0,1	-0,7	+1,4	0	-1,5	-1,5
	Liraglutid	0	+2,4	+1,6	+1,9	+3	+2,7	+5,2	+8,5	+8
	Semaglutid sc	0	-3,1	-3,4	-7,4	-9	-12,5	-5		
	Semaglutid po	0	-1,3	-5	0					
	GLP1-RA skupaj	0	-0,5	-0,7	-0,9	-0,9	-1,2	+2,6	+3,5	+3,3

Zaključek

Rezultati kažejo začeten ugoden učinek na znižanje izhodiščne telesne teže za vse GLP1-RA z izjemo liraglutida (v kombinaciji z inzulinom). V nadaljevanju zdravljenja učinek izzveni. Pri interpretaciji podatkov je potrebno upoštevati, da predstavlja naša analiza zaradi številnih omejitev (majhen vzorec, manjkajoči podatki, sočasna terapija, doslednost jemanja zdravil, kratka prisotnost peroralnega semaglutida na domačem tržišču) zgolj omejen vpogled v učinek različnih GLP1-RA na telesno težo pri bolnikih s SB tipa 2.

Reference

1. Ng ACT, Delgado V, Borlaug BA, Bax JJ. Diabesity: the combined burden of obesity and diabetes on heart disease and the role of imaging. Nat Rev Cardiol. 2021;18(4):291-304.
2. Lazzaroni E, Ben Nasr M, Loretelli C, Pastore I, Plebani L, Lunati ME, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. Pharmacol Res. 2021;171:105782.

Prispevek ni sponzoriran.

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POJAVNOST SUBAKUTNEGA TIROIDITISA MED PANDEMIJO COVID-19

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Uvod

SARS-CoV-2, ki povzroča COVID-19, vstopa v celice preko receptorja za angiotenzin konvertazo 2, čigar izraženost je celo večja v ščitnici kot v pljučih. Poleg tega se pri okužbi s SARS-CoV-2 močno odzove imunski sistem, kar lahko vpliva tudi na pojavnost bolezni ščitnice. V literaturi so opisane možne povezave med okužbo s SARS-CoV-2 in subakutnim tiroiditisom, zato smo želeli raziskati vpliv pandemije COVID-19 na pojavnost subakutnega tiroiditisa.

Metode

V klinični retrospektivni raziskavi smo pregledali zdravstveno dokumentacijo vseh bolnikov, ki so bili prvič v življenju pregledani v Ambulanti za bolezni ščitnice na Kliniki za nuklearno medicino Univerzitetnega kliničnega centra Ljubljana med 1. 4. 2019 in 29. 2. 2020 (obdobje pred COVID-19) ter med 1. 4. 2020 in 28. 2. 2021 (obdobje med COVID-19). V to ustanovo že leta prihajajo bolniki iz polovice Slovenije, v kateri živi približno milijon prebivalcev. Zaradi stabilnega področja zajemanja bolnikov lahko iz števila novih primerov ugotavljamo pojavnost posamezne bolezni. Pri vsakem bolniku so po opravljenem kliničnem pregledu, ultrazvoku ščitnice in laboratorijskih meritvah specialisti za bolezni ščitnice postavili diagnozo ščitnične bolezni.

Rezultati

V obdobju enajstih mesecev pred COVID-19 je bilo pregledanih 4844 bolnikov (1139 moških in 3705 žensk) s povprečno starostjo 54±22,9 let, v enajstih mesecih med COVID-19 pa je bilo pregledanih 4048 bolnikov (1042 moških in 3006 žensk) s povprečno starostjo 53,6±18,6 let. Med obdobjema nismo ugotovili razlik v starosti (p=0,438), je pa bil delež moških večji med pandemijo COVID-19 kot pred njo (p=0,030). V obdobju pred COVID-19 smo odkrili 65 primerov subakutnega tiroiditisa (1,2 % vseh diagnoz), medtem ko smo v obdobju med COVID-19 zabeležili 81 primerov subakutnega tiroiditisa (2 % vseh diagnoz). Pojavnost subakutnega tiroditisa je bila statistično značilno večja med pandemijo COVID-19 kot pred njo (p = 0,022).

Zaključki

Ugotovili smo, da je pojavnost subakutnega tiroiditisa statistično značilno porasla med pandemijo COVID-19. Domnevamo, da je to posledica neposrednega vpliva virusa SARS-CoV-2 na ščitnične celice ter vpliva okužbe na imunski sistem.

Reference

1. Naguib R. Potential relationships between COVID-19 and the thyroid gland: an update. J Int Med Res. 2022; 50(2):3000605221082898.

ATTACHMENT STYLES AND PERCEPTION OF GESTATIONAL DIABETES MELLITUS

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Background

Based on the Attachment theory and the Common Sense Model of illness perceptions, the current study focused on the identifying potential differences in the formation of perception about gestational diabetes mellitus (GDM) according to four attachment styles - secure, fearful, preoccupied and dismissing. Namely, illness perception can significantly influence the management of the disease, which can be a problem in GDM requiring immediate adjustment and treatment.

Method

The sample consisted of 107 women (age 32.5±4.7 years) newly diagnosed with GDM. Participants completed the Brief Illness Perception Questionnaire (BIPQ) and the Relationship Questionnaire (RQ). The Spearman correlation coefficient was used to determine the association between variables and the Mann Whitney U test was used to compare the difference among attachment styles.

Results

The expressiveness of the fearful attachment style (n=21) was associated with a more negative experience of GDM. It was associated with higher impact of GDM to their everyday life ($r=0.378$; $p<0.001$), more concerns about GDM ($r=0.324$, $p=0.001$) and higher emotional burden of the disease ($r=0.329$, $p=0.001$). Moreover, even though GDM is known as an asymptomatic disease, fearful attachment style was positively associated with experiencing the symptoms attributed to GDM ($r=0.225$, $p=0.022$). Expressions of other attachment styles were not significantly associated with dimensions of illness perception.

Conclusions

For the first time, our results show an association of attachment styles with GDM perceptions. These could affect coping with illness and could have consequences on glycemic control and pregnancy outcomes.

MIDDS (MATERNALLY INHERITED DIABETES AND DEAFNESS SYNDROME) WITH CARDIOMYOPATHY, ENDOCRINE DISORDERS AND SOME OVERLAPPING SYMPTOMS OF MELAS (MITOCHONDRIAL ENCEPHALOMYOPATHY, LACTIC ACIDOSIS, STROKE SYNDROME) – CASE REPORT

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Introduction

MIDDS is a rare monogenic disease due to a mitochondrial DNA mutation - A to G transition at position 3243 within MT-TL1 gen*. MIDDS could also be associated with neuromuscular and psychiatric manifestations, cardiomyopathy as well as renal disease, macular dystrophy and endocrine and gastrointestinal disorders and short or thin statue (1). The most common phenotype of this mutation (80% of cases) manifest as MELAS syndrome (2).

Case report

We report the case of a 42-year-old thin male who suffer from insuline dependent DM, which started at age 27 years with ketoacidosis (c peptid level was 0.14 nmol/l), complaining of muscle cramps and myalgia with normal electrolyte and myoglobin levels), headaches and depressia, at hospital admission also lactatemia of unknown origin was confirmed . Two years after that sensorineural deafness was proved. He also manifest erectile dysfunction we confirmed hypogonadotropic hypogonadism and after one year also pituitary hypothyroidism. Cardiac disease started with paroxysmal arrithmia as WPW syndrome . At age of 37 years he manifest cardiogenic shock during pneumonia. His coronary angiography was normal, on cardiac echosonography hypertophic cardiomyopathy with diastolic dysfunction was confirmed. Cardiac muscle biopsy was done and confirm the A3243G mutation in the mitochondrial gene MT-TL1 compatible with MIDDS diagnosis of very rare phenotypic mitochondrial mutation manifestation, which manifest de novo – there were no diabetes, deafness or cardiac disease in his family history. The patient is treated with insulin, hormonal replacement, ACE inhibitors , spironolactone and empagliflozine with good clinical response.

Discussion

This rare mitochondrial disease decline mitochondrial oxidation and increase ROS** which affect organs depending on energy, such as central nervous system, skeletal muscle, heart, kidney, and endocrine glands (3). Mutation could be asymptomatic or can manifest with different syndromes, some mitochodrial disease phenotypes overlap as in our patient who also has some symptoms of MELAS – except strokes (4, 5). In UK Cohort Study 6% patients were associated with combined MELAS/MIDDS overlap syndromes (6). The disease remains progressive and fatal, with lower mortality with adult disease onset. There is no curative treatment, but some antioxidants can lower ROS and rise NO production, SGLT 2 inhibitors could have promising role.

MT-TL1* gene for tRNA (Leu UUR) in mitochondria

ROS** – reactive oxygen species

References

1. Esterhuizen K, Lindeque JZ, Mason S, van der Westhuizen FH, Rodenburg RJ, de Laat P, et al. One mutation, three phenotypes: novel metabolic insights on MELAS, MIDD and myopathy caused by the m.3243A > G mutation. Metabolomics. 2021;12;17(1):10.
2. Sproule DM, Kaufmann P. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes: basic concepts, clinical phenotype and therapeutic management of MELAS syndrome. Ann N Y Acad Sci. 2008;1142:133–58.
3. Hayashi G, Cortopassi G. Oxidative Stress in Inherited Mitochondrial Diseases. Free Radic Biol Med. 2015;88:10–17.
4. Gerbitz KD, van den Ouweland JM, Maassen JA, Jaksch M. Mitochondrial diabetes mellitus: a review. Biochim Biophys Acta1995;1271(1):253–60.
5. Yatsuga S, Povalko N, Nishioka J, Katayama K, Kakimoto N, Matsuishi T. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta. 2012;1820(5):619–24.
6. Nesbitt V, Pitceathly RDS, Turnbull DM, Taylor RW, Sweeney MG, et al. The UK MRC Mitochondrial Disease Patient Cohort Study: Clinical Phenotypes Associated With the M.3243A>G Mutation–Implications for Diagnosis and Management. J Neurol Neurosurg Psychiatry. 2013;84(8):936–8.

COPPER-BASED WOUND DRESSINGS AS A NEW INTERVENTION IN CHRONIC NON-HEALING DIABETIC FOOT ULCERS

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Introduction

Chronic non-healing ulcers do not progress through the normal phases of healing in an orderly and timely manner (1). The selection of dressings is very important for the ulcer healing process; a new available option are copper-based wound dressings. Copper is known to modulate several cytokine and growth factor mechanisms and plays a key role in skin regeneration and angiogenesis (2). It enhances hypoxia inducible factor (HIF-1α) expression, which was recognized as a critical factor in wound healing (3). The purpose of the present analysis was to review the potential of copper-based wound dressings (MEDCu) in chronic non-healing diabetic foot ulcers.

Presentation of cases

Five patients (3 men and 2 women with a mean age of 65 ± 7.8 years and an average duration of type 2 diabetes of 13.6 ± 1.6 years) with chronic non-healing diabetic foot ulcers (persisting from four months to two years) were prescribed MEDCu wound dressing and included in the analysis. A standard chronic wound management protocol (debridement, local treatment, systemic antibiotic treatment, offloading and supportive angiology,

dermatology or surgical care) was followed. The wound characteristics were followed during the use of MEDCu, patient satisfaction was also observed. The mean observation period was 29.4 ± 4.0 days. In four patients, the use of MEDCu accelerated the ulcer healing process, which was observed by reducing wound surface area (WSA) by up to 46.3 ± 10.3%. In one patient, WSA and wound characteristics did not change during the use of MEDCu, which could be due to intense physical activity. Furthermore, in three patients, a regression of the wound inflammation process was observed with the use of MEDCu. All patients were very satisfied with the use of MEDCu dressings.

Conclusions

The use of MEDCu wound dressings improved chronic diabetic foot ulcer healing, which was observed as WSA reduction and attenuation of surrounding tissue inflammation. The patients were very satisfied with the MEDCu dressings. Therefore, MEDCu dressings represent a potentially effective option in the treatment of chronic diabetic ulcers.

References

1. Werdin F, Tennenhaus M, Schaller HE, Rennekampff HO. Evidence-based management strategies for treatment of chronic wounds. Eplasty. 2009;9:e19.
2. Sen CK, Khanna S, Venojarvi M, Trikha P, Ellison EC, Hunt TK, et al. Copper-induced vascular endothelial growth factor expression and wound healing. Am J Physiol Heart Circ Physiol. 2002;282(5):H1821-7.
3. Ruthenborg RJ, Ban JJ, Wazir A, Takeda N, Kim JW. Regulation of wound healing and fibrosis by hypoxia and hypoxia-inducible factor-1. Mol Cells. 2014;37(9):637-43.

DIABETIC KETOACIDOSIS IN PATIENTS WITH TYPE 2 DIABETES RECEIVING SGLT-2 INHIBITORS: A SINGLE-CENTRE CASE SERIES

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have changed in the last 5 years from convenient to ultimate treatment in type 2 diabetes (1). Their safety profile is generally good (2). Diabetic ketoacidosis (DKA) rarely occurs during SGLT-2i treatment, but can be a major concern, as a life-threatening condition. The purpose of the present study was to review the clinical cases of DKA associated with using SGLT-2i in our department to explore possible causal risk factors.

Presentation of cases

Seven patients (4 men and 3 women, aged 60±6 years; average body mass index 27.2±3.5 kg/m2) with DKA associated with SGLT-2i were hospitalised in our department in the last 4 years. Four received empagliflozin and three dapagliflozin. All were previously diagnosed with type 2 diabetes (median duration 18 years [8–33]); median HbA1c at the presentation was 8.6 % [6.9–11.6]). DKA occurred 4 days to several years after the introduction of SGLT-2i. One patient received SGLT-2i in monotherapy, others additionally received metformin (6/7), sulfonylurea/repaglinide (5/7), basal insulin

(2/7) and/or incretin therapy (2/7). The median plasma glucose at the presentation of DKA was 14.6 mmol/L [8.2–40.2], the mean pH was 7.0±0.2, HCO3- 4.2±1.8 mmol/L, with an anion gap of 27.3±4.3 mmol/L. 4/7 patients underwent urinalysis, all positive for ketones. In 4 patients, the infection was recognized as the cause of the DKA. Ketoacidosis was treated according to the standard protocol and resolved in all patients. The median fasting C-peptide was 0.29 nmol/L [0.03–0.35] and 0.40 nmol/L [0.03–0.79] after food stimulation. Autoantibodies were determined in 4/7 patients and were negative. In all patients, SGLT-2i was withdrawn without attempted rechallenge.

Conclusions

Based on our case series analysis, one of the critical triggers for the development of DKA associated with the use of SGLT-2i is infection. Therefore, general educational measures must be strictly followed, particularly stopping SGLT-2i in the setting of any acute illness or major event (surgery, etc.) (3). Other factors for the increased risk of developing DKA associated with the use of SGLT-2i could not be defined from our analysis; therefore, more studies are needed.

References

1. American Diabetes Association Professional Practice C, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl 1):S125-S43.
2. Donnan JR, Grandy CA, Chibrikov E, Marra CA, Aubrey-Bassler K, Johnston K, et al. Comparative safety of the sodium glucose co-transporter 2 (SGLT2) inhibitors: a systematic review and meta-analysis. BMJ Open. 2019;9(1):e022577.
3. Bashir J, Nalla P, Peter R, Bain SC, Chudleigh R. A case series of DKA occurring in patients receiving treatment with SGLT-2 inhibitors. Diabetes Obes Metab. 2018;20(7):1800-1.

POJAVLJANJE SRČNO-ŽILNIH DOGODKOV PRI BOLNIŠNIČNO OBRAVNAVANIH BOLNIKIH S HIPERTIROZO ZARADI BAZEDOVKE

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Znana je vzročna povezanost hipertiroze z razvojem nekaterih srčno-žilnih dogodkov (SŽD). Hipertiroza se značilno pojavlja tudi pri bazedovki, ki v primeru težjega poteka oz. potrebe po določenih terapevtskih ukrepih (intravenski tirostatik, radiojodno zdravljenje, tiroidektomija) zahteva bolnišnično obravnavo. Želela sem preveriti, če pri bolnišnično obravnavanih bolnikih (BOB) s hipertirozo zaradi bazedovke obstaja povečano tveganje za SŽD.

V retrospektivno raziskavo sem vključila v obdobju 01.01.2018-31.12.2021 prvič obravnavane bolnike z bazedovko na Kliniki za nuklearno medicino Univerzitetnega kliničnega centra Ljubljana (1113 bolnikov). Hipertirotičnih (znižan TSH, povišana pT4 in pT3) je bilo 781 bolnikov, 210 (26,9 %) BOB in 571 (73,1%) ambulantno obravnavanih bolnikov (AOB). Skupini sem s Pearsonovim χ^2-testom oz. t-testom za neodvisna vzorca primerjala po pojavnosti akutnih SŽD in prisotnosti dejavnikov tveganja.

BOB so bili glede na AOB značilno starejši (50,8±16,1 proti 44,4±14,4 let, p<0,001), prevladovali so moški (28,6 proti 20,7 %, p=0,017), imeli so večjo pojavnost arterijske hipertenzije (23,3 proti 8,2 %, p<0,001), hiperlipidemije (17,6 proti 8,1 %, p=0,001) in kajenja (35,2 proti 23,6 %, p<0,001). Indeks

telesne mase (24,6±4,5 proti 24,3±5,6 kg/m^2, p=0,851), pojavljanje sladkorne bolezni (6,2 proti 6,7 %, p=0,127), ravni TSH, pT4, pT3, antiTg in antiTPO se med skupinama niso značilno razlikovali, značilno višja pri BOB kot pri AOB je bila raven antiTSH-R (24,3±44,1 proti 9,9±16,0 IU/L, p<0,001).

SŽD je doživelo 74 (9,4 %) bolnikov (Tabela 1), značilno več BOB (54,0 % dogodkov) kot AOB (46,0 % dogodkov), p<0,001. Med skupinama v starosti ob SŽD (63,5±11,8 proti 60,8±17,9 let, p=0,063) ni bilo značilne razlike. Najpogostejši zaplet bazedovke, AF, je bil pogostejši pri BOB (p=0,034).

TABELA 1.
Pojavljanje srčno-žilnih dogodkov.

Srčno-žilni dogodek	**Vsi** N=74	**Bolnišnično obravnavani bolniki** N=40	**Ambulantno obravnavani bolniki** N=34
Akutna ishemija uda	1	0	1
Akutni miokardni infarkt	14	9	5
Atrijska fibrilacija	36	24	12
Atrio-ventrikularni blok	1	0	1
Možganska kap	3	2	1
Nestabilna angina pectoris	8	3	5
Prehodni ishemični napad	3	0	3
Tahikardna motnja srčnega ritma (brez sinusne tahikardije in AF)	7	1	6
Venska tromboza	1	1	0

Izsledki kažejo, da so se SŽD in dejavniki tveganja zanje pri BOB z bazedovko pojavljali statistično značilno pogosteje kot pri AOB.

TELEMEDICINE AND DIABETES CARE DURING COVID-19 PANDEMIC IN SLOVENIA

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Introduction

Precautionary measures during the COVID-19 pandemic facilitated use of telemedicine for routine diabetes care. Therefore, we aimed to assess the implementation of telemedicine in diabetes out-patient care nationally and across different Slovenian regions during the COVID-19 pandemic.

Methods

We analysed national and regional data of the Health Insurance Institute of Slovenia about on–site and telemedicine visits from years 2019 to 2021. Moreover, healthcare professionals' experience on telemedicine was collected using an online questionnaire, sent to all members of the Diabetology Association of Slovenia.

Results

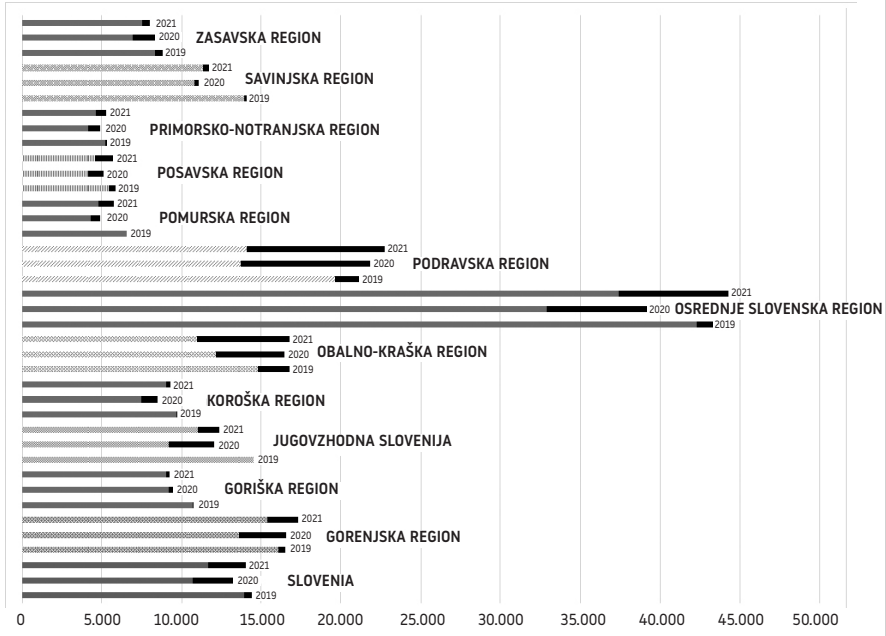
In the year 2020, the number of all diabetes out-patient visits in Slovenia was lower (n =158,339) than in year 2019 (n =173,375) or 2021 (n =168,462). The number of telemedicine visits increased 5- times from the year 2019 (n = 6,118; 3.5% of all visits) to 2020 (n = 29,695; 18.8% of all visits) with a 1.8% decline from the year 2020 to 2021. The extent of telemedicine practices varied across Slovenia (Figure), with the highest share of telemedicine visits in 2020 in Podravska (37.1%) and the lowest in Savinjska region (2.1% of all visits). The most frequently tool used was telephone call and e-mail. Telemedicine was most commonly used for elderly and pregnant women. Healthcare professionals experienced both advantages (mainly good accessibility for patients and cost–effectiveness) and disadvantages (mainly personal burden and worse treatment control) with telemedicine approach.

Discussion and conclusion

During the COVID-19 pandemic, use of telemedicine increased profoundly, however, its implementation in daily clinical practice is not increasing after the year 2020. Experience and implementation rate varied across regions and practices. Nevertheless, telemedicine offers useful tools that can be well implemented in diabetes care also outside the COVID-19 frame, complementary to on-site visits, in certain groups of individuals and specific settings, yet improvements in many aspects are needed.

FIGURE 1.

Number of on-site and telemedicine visits in Slovenia and its regions between years 2019 and 2021.



Legend:

Every region has its own color for on-site (first part of the row) and telemedicine (second part of the row) visits. The columns of regions represent absolute number of visits, but the column Slovenia represents the average absolute number of all regions.

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REAL WORLD DATA CONFIRMS ASSOCIATION OF FLASH GLUCOSE MONITORING-DERIVED TIME IN RANGE AND HBA1C

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Background and aims

Flash glucose monitoring (FGM) has become widely used and recognized as a "beyond glycated haemoglobin (HbA1c)" tool. According to the consensus recommendations, several metrics, such as time in range (TIR), time above range (TAR) and time below range (TBR) can be used. Associations between TIR (70 – 180 mg/dL; 3.9 – 10 mmol/L) and diabetes complications have been investigated to corroborate the relationship between TIR and HbA1c. However, most data were gathered by paired HbA1c and %TIR metrics from frequent self-monitoring of blood glucose (SMBG) data or data provided by continuous glucose monitoring (CGM). Currently, the most frequently used device in clinical practice is FGM. Therefore, device (e.g., FGM) specific TIR-HbA1c relations should be established. This pilot study aimed to establish real world data-based correlations between several metrics measured by FGM and well-established laboratory parameter of glycaemic control, HbA1c.

Methods

Included subjects (n=32, age 59 ± 17 years) were both Type 1 (64%) and Type 2 diabetes patients, treated with insulin, who had central-laboratory measurements of HbA1c. They were monitored for a up to 20-month period in their daily life through commercial FGM devices, reimbursed by the National Health System. FGM metrics were calculated and compared with each other and with HbA1c cross-sectionally. Paired FGC metrics and HbA1c were evaluated by Pearson's correlation coefficient.

Results

The average TIR and HbA1C were 63.9±20.4 % and 7.5 ± 1.2 %, respectively, and were linearly correlated. The correlation coefficient (R) of mean TIR with mean HbA1C was –0.802; P<0.01 (2-tailed). For every absolute 10% change in %TIR, there was a 0.85 % change in HbA1c (Figure 1). TIR was strongly correlated with TAR (R= –0.995; P<0.01), but, not with TBR (R= –0.066, NS). HbA1c was strongly correlated with TAR (R= –0.790; P<0.01), but not significantly with TBR (R= –0.025, NS).

Conclusions

Real world data demonstrated a strong linear correlation between %TIR captured by FGM and HbA1c. The assessment of device-specific TIR–HbA1c relationship in real-life conditions is important for diabetologists to gain trust and rely on FGM-derived metrics in every day clinical practice.

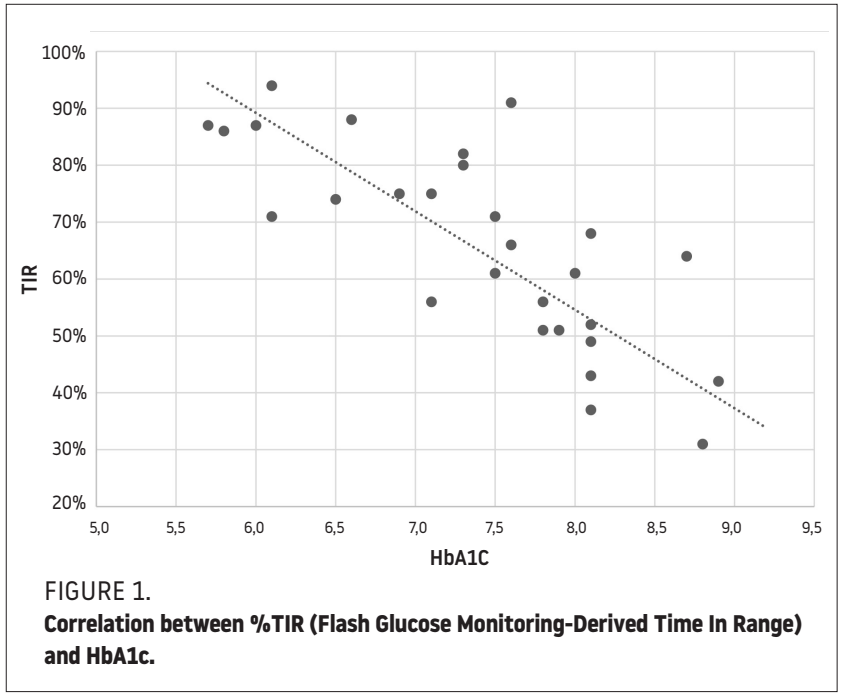

FIGURE 1.
Correlation between %TIR (Flash Glucose Monitoring-Derived Time In Range) and HbA1c.

References

1. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42:1593–603.
2. Yaron M, Roitman E, Aharon-Hananel G, Landau Z, Ganz T, Yanuv I, et al. Effect of Flash Glucose Monitoring Technology on Glycemic Control and Treatment Satisfaction in Patients With Type 2 Diabetes. Diabetes Care. 2019;42:1178–84.
3. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of Real-time Continuous Glucose Monitoring With Glycemic Control and Acute Metabolic Events Among Patients With Insulin-Treated Diabetes. JAMA. 2021;325:2273–84.

KRONIČNA LEDVIČNA BOLEZEN PRI SLADKORNEM BOLNIKU – JO PODCENJUJEMO?

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Uvod

Sladkorna bolezen je kronična metabolna bolezen, njena pojavnost pa po svetu vse bolj narašča (1). Osebe s sladkorno boleznijo ogrožajo zapleti, najbolj pogosto srčno-žilna obolenja, retinopatija in okvara ledvic (1). Slednja predstavlja glavni vzrok kronične ledvične bolezni, njeno zdravljenje pa predstavlja velik zdravstveni izziv (2). Pristop mora biti multidisciplinaren, pri zdravljenju pa sledimo sodobnim smernicam Združenja za nefrologijo (KDIGO) (2). Osebe s sladkorno boleznijo in ledvično boleznijo zdravimo z novejšimi antihiperglikemičnimi zdravili, predvsem so se na tem področju izkazali zaviralci natrij-glukoznih transporterjev (SGLT2 zaviralci) (3). Raziskave s SGLT2 zaviralci so pokazale odlične ledvične izide ter manjšo umrljivost pri osebah s kronično ledvično boleznijo. (3)

Ali na ledvično bolezen pomislimo dovolj pogosto?

V Ambulanti za diabetike v Kopru smo se odločili, da na vzorcu bolnikov preverimo, koliko dejansko je ledvične okvare in ali bolniki prejemajo sodobna zdravila z ugodnimi učinki na ledvice*.

Metode

Med 1. 5. in 31. 7. 2022 smo pregledali kartoteke naključno izbranih bolnikov. Številka predstavlja približno 10% bolnikov, zdravljenih v naši ambulanti. Pregledali smo laboratorijske izvide kreatinina in ocenjene glomerulne filtracije (CKD-EPI), morebitno že postavljeno diagnozo ledvične bolezni ter napotitev k nefrologu, bolnikove ostale zaplete in zdravila, ki jih prejema.

Rezultati

Analizirali smo 700 kartotek bolnikov. Povprečna starost bolnikov je bila 68 let, 57% je bilo moških, povprečni Hba1c je bil 7,2 %. Sladkorna bolezen je v povprečju trajala 12,5 let. Diagnoza ledvične bolezni je bila postavljena pri 91 bolnikih (13%), po pregledu podatkov pa je kriterijem za postavitev diagnoze (po KDIGO) ustrezalo 234 bolnikov (34%). Manj kot četrtina je imela še ostale zaplete (ASŽB n=170 (24%), SP n=103 (15%) in retinopatija n=81 (12%)). Pogledali smo še, ali bolniki prejemajo terapijo, ki ugodno vpliva na ledvične bolezni. Od bolnikov, ki so imeli postavljeno diagnozo ledvičnega zapleta, je terapijo s SGLT2 zaviralci prejemalo 34 bolnikov (37%), od tistih, ki ustrezajo kriterijem, vendar diagnoze še nimajo zavedene, pa je SGLT2 zaviralec prejemalo 98 bolnikov (42%).

Zaključek

Rezultati so pokazali, da (pre)pogosto ne postavimo diagnoze kronične ledvične okvare dovolj zgodaj. Postavitev zgodnje diagnoze kronične ledvične bolezni in uvedba terapije s SGLT2 zaviralci pa je pomembna pri preprečevanju progresa ledvičnih zapletov. Verjamemo, da nam bodo rezultati pregleda pomagali k boljši obravnavi bolnikov s sladkorno boleznijo in kronično ledvično okvaro.

Literatura

1. WHO - Diabetes. Pridobljeno 30.8. 2022 s spletne strani https://www.who.int/health-topics/diabetes
2. Garabed Eknoyan, Norbert Lameire, David C. Wheeler, Michel Jadoul, Wolfgang C. Winkelmayer, et al. KDIGO 2022 Clinical practice guidelines for diabetes management in chronic kidney disease. Pridobljeno s spletne strani 30.8. 2022 https://kdigo.org/wp-content/uploads/2022/03/KDIGO-2022-Diabetes-Management-GL_Public-Review-draft_1Mar2022.pdf
3. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020;383(15):1436-1446.

*Pregled bolnikov smo opravili v sodelovanju s podjetjem AstraZeneca

SPREMEMBA NOHTA NA NOGI – POT DO DIAGNOZE

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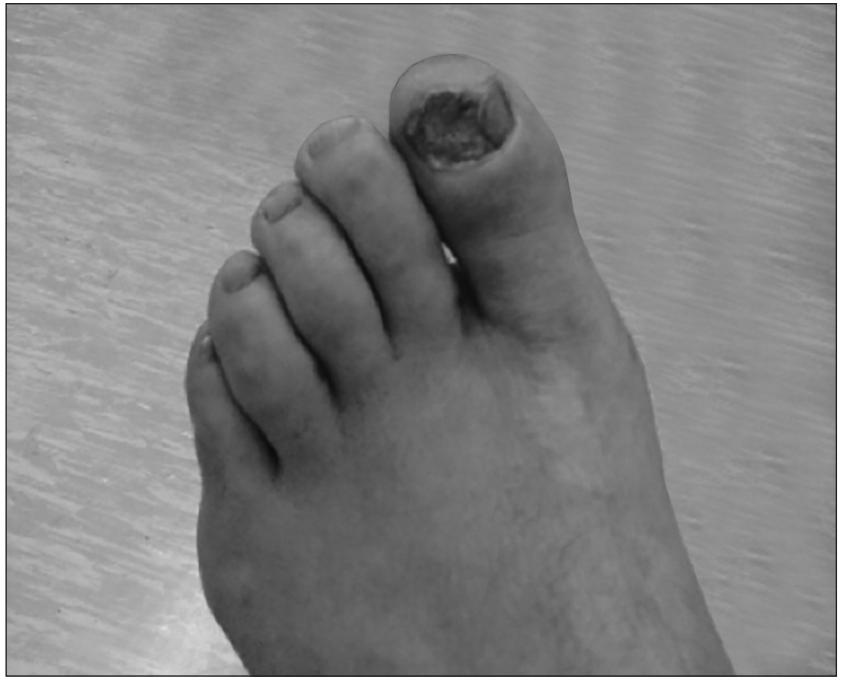
Uvod

Težave z nohti so pri diabetikih pogoste. Navadno so posledica okvare živcev ali prekrvitve spodnjih okončin. Na njih se lahko razvijejo tudi okužbe, najpogosteje glivične(1). Včasih pa na pogled nedolžna okužba razvije težke posledice.

Prikaz primera

63-letni bolnik se v Ambulanti za Diabetike Koper obravnava od leta 2011. Pri zdravljenju ne potrebuje terapije, upošteva nefarmakološke ukrepe. V letošnjem letu je ambulanto obiskal zaradi sprememb na nohtu prvega prsta leve noge. Preden je obiskal našo ambulanto, je bila sprememba nohta prisotna že približno pol leta, prejemal je antibiotike. Stanje se ni izboljševalo.



Ob obravnavi v naši ambulanti je bila na nohtu prisotna razjeda nohta-noht je deloval »požrt«, rana je bila brez sekrecije ali znakov vnetja. Ob prvi obravnavi smo opravili diagnostiko nevropatije, ki ni bila prisotna, stopalni pulzi so bili dobro tipni. Napotili smo ga na pregled h kirurgu. Opravljen je bil RTG prsta, ki je pokazal znake akutnega osteomielitisa. Uvedena je bila dvotirna antibiotična terapija, ki jo je gospod prejemal 8 tednov. Odvzet je bil tudi bris, iz katerega so porasle številne bakterije, ki so bile občutljive na uvedeno terapijo. Svetovana je bila kontrola pri žilnem kirurgu, ki pa je gospod ni opravil. Kljub terapiji, se stanje ni izboljševalo, zato smo gospoda napotili še na dermatološki pregled. Ta je svetoval dodatno diagnostiko ter antibiotična mazila. Ob ponovni napotitvi k žilnemu kirurgu, so gospodu amputirali del prsta. Izvid histopatološkega pregleda govori, da gre za invazivni ploščatocelični karcinom, ki je bil odstranjen v zdravo. Zaradi blage limfocitne infiltracije je svetovana še odstranitev varovalne bezgavke.

Zaključek

Rakava obolenja so pri sladkornih bolnikih pogostejša kot v populaciji brez sladkorne bolezni. Zaradi slabšega celjenja ran in pogostejših okužb, se pogosteje pojavljajo kožni malignomi. V primerjavi z zdravo populacijo je preživetje pri kožnih karcinomih slabše (2), zato je pomembno, da ob nenavadnih ranah pomislimo tudi na to diagnozo. Zgodnje prepoznavanje je ključno.

Literatura

1. Rich, P. Nail Changes due to diabetes and other endocrinopathies. Dermatol Ther. 2002;15:107-110.
2. Ederaine SA, Lopez-Dominguez J, Harvey JA, Mangold AR, Cook CB, et al. Survival and glycemic control in patients with co-existing squamous cell carcinoma and diabetes mellitus. Future Sci OA. 2021;7(5):FSO683.

SELF-REPORTED PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR IN OLDER ADULTS WITH DIABETES

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Background

Despite proven benefits of regular physical activity (PA) in diabetes patients, physical inactivity and sedentary lifestyle is increasing across all age groups. The aim of the present study was to examine self-reported PA and sedentary behaviour in older adults with type 1 diabetes (T1D) and type 2 diabetes (T2D) patients and possible differences between diabetes types. The associations of PA and sitting time (ST) with glycaemic control and BMI were also explored.

Methods

This cross-sectional cohort non-exposure study included 117 patients, aged ≥60 years, treated with insulin regimens. Statistical analyses were conducted on data gathered by the International Physical Activity Questionnaire - IPAQ. Data was presented as mean ± standard error of mean (SEM).

Results

Patients were aged 71.6 ± 1.1 years, majority had T2D (75%). T1D patients were active 162 ± 32 minutes weekly and sedentary 4.45 ± 0.7 hours daily,

while T2D were active 72 ± 12 min and sedentary 6.71 ± 0.9 h (p <0.01 for both). T1D patients had longer duration of vigorous PA (up to 7.2-fold; p <0.05). PA and BMI were associated in subjects with T1D (r = -0.5; p <0.01), however, in T2D subjects sitting time (ST) and BMI were associated (r = 0.2; p <0.05). Regular physical activity was not associated with improved glycaemic control. Only the patients achieving >1500 metabolic equivalent-minutes weekly had significantly lower HbA1c (7.9% ± 1.6% vs. 7.3% ± 1.2% (p <0.05).

Conclusion

The results suggest that older age itself is not a barrier to engagement in PA. Older T1D patients were in general more active and less sedentary compared to T2D counterparts and performed longer duration of vigorous PA, whereas T2D patients engaged in mostly low or moderate PA, e.g. walking. The expected beneficial affect of PA on glycaemic control was observed only in the very active older diabetic patients. Therefore, tailored advice targeting physical inactivity is important during lifelong diabetes education, since it can guide older adults of both diabetes types towards better metabolic health.

References

1. Saint-Maurice PF, Graubard BI, Troiano RP, Berrigan D, Galuska DA, Fulton JE, et al. Estimated Number of Deaths Prevented Through Increased Physical Activity Among US Adults. JAMA Intern Med. 2022. 182(3):349–352.
2. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, et al. Impact of Physical Activity on Glycemic Control and Prevalence of Cardiovascular Risk Factors in Adults With Type 1 Diabetes: A Cross-Sectional Multicenter Study of 18,028 Patients. Diabetes Care. 2015;38(8):1536–1543.
3. Johansen MY, MacDonald CS, Hansen KB, Karstoft K, Christensen R, Pedersen M, et al. Effect of an Intensive Lifestyle Intervention on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Clinical Trial. JAMA. 2017;318:637–46.

STAROSTNO POGOJENE SPREMEMBE V NIVOJIH KRVNIH MAŠČOB IN GLUKOZE TER NJIHOVA POVEZAVA Z UPORABO ZDRAVIL IN SMRTNOSTJO: OPAZOVALNA RAZISKAVA

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Predstavljamo analizo dinamike krvnih maščob (KM) in glukoze (G) glede na starost in spol, pri čemer so nas zanimali vplivi uporabe antidiabetičnih in hipolipemičnih zdravil ter smrtnosti na analizirane meritve. Osnovna analiza temelji na anonimiziranih podatkih Zdravstvenega doma Dr. A. Drolca za holesterol (celokupni holesterol, LDL, HDL, TG) in glukozo v obdobju 2008–

2019 (506.083 laboratorijskih testov, 63.606 pacientov). Glede na znano povezavo dislipidemije in hiperglikemije (1) smo se vprašali ali se motnji pojavljata sočasno in ali je razlika po spolu. V drugi fazi raziskave smo vključili anonimizirane podatke porabe zdravil Zavoda za zdravstveno zavarovanje Slovenije za obdobje 2013–2018 za dve anatomsko terapevtski skupini (ATC A10 – zdravila za sladkorno bolezen in ATC C10 – hipolipemiki) (392.171 različnih pacientov). Zanimalo nas je, ali in kako se laboratorijski podatki spreminjajo glede na porabo omenjenih skupin zdravil. V zadnji fazi raziskave smo dodali še podatke o smrtnosti Statističnega urada republike Slovenije za leto 2018 z namenom analize vpliva umrljivosti na statistiko meritev KM in G.

Zaključki

Ugotovili smo, da se najvišji procent populacije s povišanimi vrednostmi G pojavlja približno 20 let kasneje kot največji procent populacije z hiperlipidemijo. Uporabili smo tri različne podatkovne baze, kar ni dopuščalo longitudinalne raziskave, vendar je omogočalo dokazati, da so profili KM in G v populacijski statistiki kvalitativno spremenjeni z zdravili in s smrtnostjo. Zaznali smo dve prelomni točki, prva v starosti 55-59 let ustreza največjemu porastu uporabe zdravil in druga sovpada z naglim porastom smrtnosti v starosti 75-79 let (2). V kasnejši, dodatni študiji smo z metodo matematičnega modeliranja opozorili še na nekatere ključne celične mehanzme v celicah beta, ki lahko ob kroničnih pogojih hiperlipidemije vodijo v povišano bazalno izločanje inzulina in pomanjkanje inzulinske sekrecije po hrani (3).

References

1. Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature. 2019;576:51–60.
2. Markovič R, Grubelnik V, Vošner HB, Kokol P, Završnik M, Janša K, Zupet M, Završnik J, Marhl M. Age-Related Changes in Lipid and Glucose Levels Associated with Drug Use and Mortality: An Observational Study. J Pers Med. 2022;12(2):280.
3. Grubelnik V, Zmazek J, Završnik M, Marhl, M. Lipotoxicity in a Vicious Cycle of Pancreatic Beta Cell Exhaustion. Biomedicines. 2022;10:1627.

ORAL SEMAGLUTIDE IN COMBINATION WITH METFORMIN IS AN EFFECTIVE TREATMENT OF SYMPTOMATIC HYPERGLYCEMIA IN PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES

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Introduction

Symptomatic hyperglycemia in newly diagnosed type 2 diabetes demands prompt pharmacological treatment, generally with a dual oral antihyperglycemic regime or insulin (1). Due to good effectiveness, relative safety and low cost, sulphonylureas are preferable antihyperglycemic agents in addition to metformin. Renal impairment and high risk of hypoglycemia limit its use and frequent dose adjustment is required. Oral semaglutide is a novel antihyperglycemic with proven clinical effectiveness and safety even in case of renal or liver impairment (2). Due to its mechanism through the incretin system, it does not cause hypoglycemia. Could oral semaglutide be an alternative choice along with metformin for the treatment of symptomatic hyperglycemia in newly diagnosed type 2 diabetes?

Methods

The study was conducted from April 2022 to August 2022 in the outpatient diabetes clinic of the University Medical Centre Ljubljana. Nine patients with

newly diagnosed type 2 diabetes and symptomatic hyperglycemia without previous antihyperglycemic treatment were enrolled and put on a dual therapeutic regimen with metformin and oral semaglutide. The titration was performed according to the protocol provided by the manufacturer. The follow-up was scheduled between 30 and 45 days after the initial visit. For the statistical analysis, we used the t-test.

Results

Of nine patients three were females. The mean age was 44 years (SD+/-7,6). Mean baseline blood glucose was 13,8 mmol/L (SD+/-1,7). All patients reported symptoms of hyperglycemia. At the follow-up, six patients had received a cumulative daily dose of metformin 2000 mg, three 1000 mg. Five patients received oral semaglutide 7 mg and four patients 3 mg per day. Hyperglycemic treatment was effective. Baseline HbA1c 10,7 % (SD+/-2,0) has decreased to 8,9 % (SD+/-1,3), change -1,9% (SD+/-1,5; 95 % CI 0,7, 3,0; p<0,006). The effect on bodyweight was evident, albeit statistically not significant, with baseline body mass index 35,9 kg/m2 (SD +/- 7,1) reduced to 33,6 kg/m2 (SD +/-6,0), change -2,3kg/m2 (SD +/-3,4; 95 %, CI -0,6, 5,1; p=0,104). All the reported hyperglycemia-associated symptoms resolved. Treatment was generally well tolerated. One patient complained of mild gastrointestinal symptoms. No patients discontinued with treatment.

Conclusions

Oral semaglutide in combination with metformin offers a safe and effective alternative treatment of symptomatic hyperglycemia in patients with newly diagnosed type 2 diabetes.

References

1. Janež A. Zdravljenje hiperglikemije z zdravili. Urednica Pongrac Barlovič D. Slovenske smernice za klinično obravnavo sladkorne bolezni tipa 2. Ljubljana: Diabetološko združenje Slovenije; 2022.
2. Aroda VR, Rosenstock J, Terauchi Y, Altuntas Y, Lalic NM, Morales Villegas EC, Jeppesen OK, Christiansen E, Hertz CL, Haluzík M; PIONEER 1 Investigators. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-1732.

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