

BRINGING THE LATEST IN PAEDIATRIC ENDOCRINOLOGY TO YOU

Managing type 1 diabetes

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Welcome

I start this issue with a reminder to you all to look at the exciting, diverse online programme for the 61st Annual ESPE Meeting (see page 9). It includes plenary lectures, Meet the Expert sessions, symposia and the ever-popular 'How Do I?' talks, and much else besides, with a spread of basic, translational and clinical science. There is something for everyone.

The meeting takes place in The Hague, The Netherlands, on 21–23 September. Make sure you take advantage of early bird rates and register by 17 July. See www.eurospe.org/events-espe/espe-2023-annual-meeting.

Elsewhere in this issue, we look at the latest approaches to the management of type 1 diabetes mellitus, and thank all the authors who have contributed to this topic.

On **page 4**, John S Pemberton relates his experience in the use of bouts of physical activity between meals to improve blood glucose time in range. He concludes that providing complementary education about the benefits of short bouts of fun activities in improving glucose status may appeal to the majority of young patients.

Consensus recommendations have recently been published for automated insulin delivery technologies in clinical practice. We are delighted that Revital Nimri, lead author from the consensus group, presents a summary of the important points on **page 6**.

On **page 7**, Dr IPS Kochar summarises the current issues associated with the use of pancreatic transplantation. Although this approach has much potential, various points need to be addressed before it can be a first-line therapy.

We are reminded of ESPE's important role in supporting research on **page 8**. Anu Bashambo received the 2019 Henning Andersen Award in basic research for her work on a new stem cell model to study sex determination, which she describes here with co-author Ken McElreavey. The research itself received funding from the ESPE Research Unit. Find out how to apply for ESPE grants at www.eurospe.org/grants-awards.

Details of forthcoming ESPE dates and deadlines can be found on **pages 9 and 10**, including the Science Symposium in October, and the ESPE Connect Webinars.

If you have any comments or suggestions for the content of your newsletter, and how it can best serve the needs of ESPE members, please email me at the address below. I look forward to hearing from you.

Antje Garten

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New Editor for ESPE News

We welcome Antje Garten as our Editor, and thank Sarah Ehtisham for all her work during her term of office.

Antje is a senior researcher at the Center for Pediatric Research, Hospital for Children and Adolescents, Leipzig University, Germany. Her research focuses on growth factor signalling and mechanisms of lipid accumulation. She has been an Editorial Board member since 2018.



Please contact her with ideas and comments for the newsletter at Antje.Garten@medizin.uni-leipzig.de.

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IN MEMORIAM



Henk K A Visser

We are sad to report the death of Henk K A Visser, a founding member of ESPE, and an Honorary Member of the Society since 2002. He was instrumental in the early development of ESPE, from a small club of 28 friends to today's global scientific society.



You can read the full obituary at www.eurospe.org/about/announcements/obituary

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ESPE 2023

21–23 September 2023
The Hague,
The Netherlands

**Global Challenges
in Paediatric
Endocrinology**

Early bird registration deadline: **17 July 2023 (23.59 BST)**

Find out more on **page 9**

Bringing you recent highlights from the world of research

Empagliflozin or linagliptin in childhood type 2 diabetes

Despite an increase in the incidence of type 2 diabetes in children, treatment options are limited. Laffel *et al.* evaluated the efficacy of empagliflozin and linagliptin as monotherapies to reduce glycated haemoglobin (HbA1c) in a double-blind, placebo-controlled trial in 158 patients from 15 countries.

Over the course of 26 weeks, HbA1c was reduced by a mean additional 9.2mmol/mol in patients treated with empagliflozin versus placebo ($P=0.012$). Those receiving linagliptin showed a non-significant reduction in HbA1c versus placebo (-3.8mmol/mol ; $P=0.29$). Hypoglycaemia was more common in those receiving treatment versus placebo, but no severe hypoglycaemic events were reported.

The authors conclude that empagliflozin may offer a new treatment option for children with type 2 diabetes.



Read the full article at Laffel *et al.* 2023
Lancet Diabetes & Endocrinology 11 169–181

Verapamil and β cell function in paediatric type 1 diabetes

In this paper by Forlenza *et al.*, the CLVer Study Group report partial preservation of pancreatic β cells with the use of verapamil in new-onset type 1 diabetes mellitus (T1DM). A total of 88 children and adolescents aged 7–17 years, with newly diagnosed T1DM, were enrolled in a multicentric, randomised control trial in the USA. Of these, 47 children received once-daily oral verapamil, starting within 1 month of diagnosis and continuing until 52 weeks.

The mean adjusted between-group difference in C-peptide area under the curve for those receiving verapamil versus placebo was 0.14pmol/ml (95% CI, 0.01–0.27pmol/ml; $P=0.04$). This equated to a 30% higher C-peptide level at 52 weeks with verapamil. The glycated haemoglobin level after 52 weeks was 6.6% among the verapamil group compared with 6.9% in the placebo group ($P>0.05$). There was no difference in adverse events between the two study groups.

The authors propose further studies to determine the durability of C-peptide improvement and optimal duration of therapy with verapamil.



Read the full article at Forlenza *et al.* 2023
JAMA 329 990–999

SEC16B: a novel candidate gene in osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a group of disorders characterised by low bone mass, recurrent fractures, and skeletal deformities. The genetic causes are heterogeneous, with frequent pathogenic variants found in the genes that encode type I collagen. This structural protein is a major constituent of the extracellular matrix of bone tissue, and represents the core element for bone formation. Other genetic variants have been found in genes involved in the processing and assembly of type I collagen. For some patients, a causative genetic defect has not yet been identified.

El-Gazzar *et al.* report a child with skeletal dysplasia resembling OI and a homozygous mutation in the *SEC16B* gene: an endoplasmic reticulum (ER)-associated protein, the biological significance of which is, as yet, unknown. Patient-derived fibroblasts showed defects in collagen trafficking and processing that lead to ER stress, increased autophagy, and apoptosis. At the molecular level, the variant *SEC16B* gene showed altered levels of expression. *SEC16B* can be considered a new candidate gene in OI.



Read the full article at El-Gazzar *et al.* 2023
EMBO Molecular Medicine 15 e16834

Ratio of IGF-1 to IGFBP-3 in diagnosis of GH deficiency

To study the usefulness of the molar ratio of serum insulin-like growth factor-1 (IGF-1) to IGF-binding protein-3 (IGFBP-3) in the diagnosis of growth hormone deficiency (GHD), Haj-Ahmad *et al.* conducted a cross-sectional observational study in 235 children with short stature over a 7-year period. The mean age for the study group was 10.7 \pm 3.3 years. The study participants were classified into GHD ($n=64$) and non-GHD ($n=171$) groups.

The data suggested that a low molar ratio of serum IGF-1 to IGFBP-3 showed the highest sensitivity (87.5%) for GHD, and the specificity was 83.0%. However, the combination of low IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio had the highest specificity for GHD (97.7%), and 100.0% specificity for non-GHD causes.

The authors thus concluded that the serum IGF-1/IGFBP-3 ratio may serve as a promising marker for the diagnosis of GHD and that it is a potential area of research for future studies.



Read the full article at Haj-Ahmad *et al.* 2023
Journal of Clinical Endocrinology & Metabolism 108 986–994

Physical activity between meals in diabetes management

John S Pemberton discusses the use of moderate-intensity physical activity between meals to treat high glucose levels for children and young people with type 1 diabetes.



John S Pemberton

International consensus guidance for children and young people (CYP) with type 1 diabetes mellitus (T1DM) provides extensive recommendations for hypoglycaemia (<3.9mmol/l) prevention, while promoting the long term benefits of being physically active throughout life.¹ Educational programmes² and opportunistic teaching translates the recommendations into clinical practice,² which may exacerbate the fear of hypoglycaemia and reduce some individuals' motivation to partake in physical activity, whilst missing the positive reinforcement from short term rewards.³

A more positive perspective on the value of physical activity emerges upon considering the benefits of moderate-intensity activity undertaken after eating. A secondary analysis of 120 CYP with T1DM by Riddell *et al.*⁴ suggests that using physical activity to lower high glucose levels is an effective strategy. The CYP performed 45–60 minutes of moderate-intensity cycling or walking, which was completed 100–240 minutes after a meal with usual prandial insulin.⁴ Those starting with a blood glucose level above 10.6mmol/l experienced a median drop of 6.1 mmol/l, with <15% experiencing hypoglycaemia.⁴

Using these data, the International Society for Adolescent and Pediatric Diabetes (ISPAD) 2022 Exercise Guideline¹ recommends that 'Moderate intensity aerobic activity, such as walking and cycling for 15–45 minutes between meals, safely lowers glucose levels >10.6mmol/l (190 mg/dl) (B).'

“
Analysis of the first 100 graduates from the CGM Academy reported that the implementation of GAME was the strongest predictor of time in range”

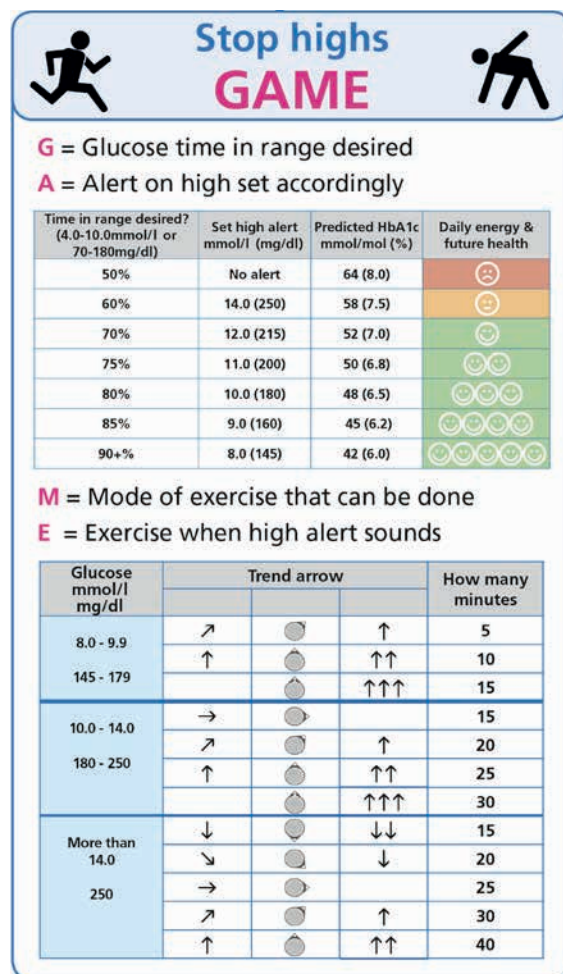


Figure. GAME: using moderate-intensity physical activity between meals to lower glucose levels. HbA1c, glycated haemoglobin.

Table. Risks when using moderate-intensity physical activity to lower the glucose level between meals, and strategies that can be taught to overcome them.

Risk	Strategy to overcome the risk
Delayed hypoglycaemia in the 2 hours after the PA	Aim to lower the glucose level to just less than 10.0mmol/l
Variability in glucose-lowering response between individuals and for the same individual on different days	Educating that 10–15 minutes of moderate-intensity PA lowers the glucose by 2.0mmol/l or the algorithm in GAME (see Figure) is a heuristic that requires trial and error to individualise
Missing hypoglycaemia due to the prolonged lag time of CGM readings following PA-induced drops in glycaemia	Aim to lower the glucose level to just less than 10.0mmol/l to prevent missing hypoglycaemia (<3.9mmol/l)
Glucose level rise if the exercise is too vigorous	PA only recommended in the 4 hours after meals; increase in glucose level is only a risk when PA is performed in the fasted state
Glucose level higher than 15.0mmol/l	Follow the ISPAD 2022 Exercise Guidelines ¹ <ul style="list-style-type: none"> • Ketones >1.5mmol/l: follow usual ketone advice and avoid PA • Ketones 1.1–1.4mmol/l: give ½ correction dose by pen and wait 60 minutes to reassess • Ketones 0.6–1.0mmol/l: give ½ correction dose by pen and wait 15 minutes to start the PA • Ketones <0.6mmol/l: consider ½ correction dose and start PA
Indiscriminate use by CYP with T1DM and their carers	Teach parents to agree the use of the strategy in advance with the child or young person; it is an optional tool to be used as and when it suits the individual, not the person supporting their care
Use with AID systems	Teaching the strategy may be valuable following underestimation of inputted carbohydrates; however, it should be applied with caution because it runs parallel with automated corrective insulin

AID, automated insulin delivery; CGM, continuous glucose monitoring; PA, physical activity.

Continued on page 5

Continued from page 4

Simplifying the message

The Birmingham Children's Hospital's 'CGM Academy' simplifies this message by teaching that 10–15 minutes of brisk walking, biking or dancing to YouTube between meals drops the glucose level by ~2.0mmol/l.⁵ The teaching was updated following patient feedback to become 'GAME' (see Figure, **page 4**).⁶ Analysis of the first 100 CYP with T1DM graduating from the CGM Academy reported that the implementation of GAME was the strongest predictor of time in range (3.9–10.0mmol/l) at 6 months after education.⁵

However, there are several risks when using moderate-intensity physical activity to lower glucose between meals, summarised in the Table (**page 4**).

How it works

Using moderate-intensity activity to lower high glucose levels between meals works by:

- speeding up the onset of insulin action, which is especially useful when insulin is administered at or after a meal
- increasing blood flow to the muscles, which augments the relative proportion of insulin used by the muscles instead of being degraded by the kidneys, and is

particularly effective following the underestimation of carbohydrates

- promoting insulin-independent uptake of glucose into the muscle cells, which is helpful following the insulin resistance impact of a high-fat meal.

In summary

Providing complementary education regarding the improvement of time in range by undertaking shorter bouts of fun activities may appeal to the majority, rather than solely focusing on hypoglycaemia mitigation and the long term benefits of living an active lifestyle.

John S Pemberton

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Author's declaration

The work did not receive any specific funds. Conflicts of interest: the author worked for Medtronic from 2011 to 2016 and has received personal fees from Roche.

References

1. Adolfsson et al. 2022 *Pediatric Diabetes* **23** 1341–1372.
2. Price et al. 2016 *Diabetic Medicine* **33** 192–203.
3. Hajat et al. 2019 *npj Digital Medicine* **2** 1–6.
4. Riddell et al. 2019 *Pediatric Diabetes* **20** 99–106.
5. Pemberton et al. 2021 *Pediatric Diabetes* **22** 249–260.
6. Pemberton et al. 2022 *Pediatric Diabetes* **23** 1045–1056.

Test yourself with e-Learning

The ESPE–ISPAD (International Society for Adolescent and Pediatric Diabetes) e-Learning web portal is an interactive resource on paediatric endocrinology and diabetes mellitus. Use it, free of charge, to expand your knowledge of paediatric endocrinology.



For more details, see www.eurospe.org/education/e-learning



Register for free access at www.espe-elearning.org

This issue's clinical case highlight

Can you identify MODY (maturity-onset diabetes of the young)? Hollie was born macrosomic, birth weight 4.2kg, at 38 weeks gestation. She had neonatal hypoglycaemia, blood glucose 0.8mmol/l (14mg/dl), that persisted beyond the first week of life, and required treatment for 6 months with diazoxide and chlorothiazide.

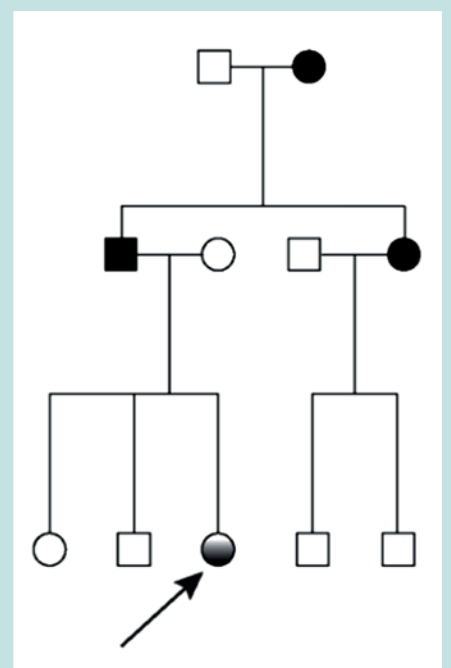
Hollie's **father** was diagnosed with type 2 diabetes (T2DM) at age 26, body mass index (BMI) 28kg/m², treated with sulphonylureas, glycated haemoglobin (HbA1c) 53mmol/mol (7.0%). Her **paternal aunt** had been diagnosed with T1DM at age 17, during routine screening, and had been treated with insulin since diagnosis, BMI 25kg/m², HbA1c 66mol/mol (8.2%). Hollie's **paternal grandmother** had been diagnosed with T2DM in her early 40s, BMI 27kg/m², tablet-treated, HbA1c 45mmol/mol (6.3%).

Which features indicate this could be a family with MODY?

Tick all that apply

- | | |
|--|---|
| <input type="checkbox"/> The macrosomia at birth | <input type="checkbox"/> The HbA1c in those with diabetes |
| <input type="checkbox"/> The autosomal dominant family history of diabetes | <input type="checkbox"/> The neonatal hypoglycaemia |
| <input type="checkbox"/> None of the above | |

For the answer, see **page 10**.



Hollie's family tree indicating an autosomal dominant family history of diabetes across two generations.

Automated insulin delivery: what you need to know

Revital Nimri highlights key points from the new consensus recommendations for automated insulin delivery (AID) technologies in clinical practice.



Revital Nimri



All individuals with type 1 diabetes mellitus should be considered as potential users of AID systems"

Many consider AID to be the most promising development in the management of type 1 diabetes mellitus (T1DM) since the discovery of insulin a century ago.

Although the concept of AID has existed for several decades, recent advancements in continuous glucose monitoring (CGM) technology have enabled the development of more complex control algorithms. These algorithms automatically adjust insulin doses delivered by insulin pump based on real-time sensor glucose levels, allowing more precise and effective diabetes management. Today, the available AID systems have become an integral part of diabetes management, while further new systems are under development.

Randomised controlled studies have consistently shown that AID implementation across all available devices leads to a 9–16% increase in time in range, a decrease in glycated haemoglobin levels of 0.3–0.5%, and either no change or a reduction in the amount of time spent in hypoglycaemia. Recent real-world data, from thousands of users with variable characteristics, demonstrated similar results. Furthermore, these systems have been effective in reducing the diabetes self-management burden, leading to improvement in overall quality of life.¹

In 2021, the faculty of Advanced Technologies and Treatments for Diabetes (ATTD) initiated a convention of 75 experts to establish clinical recommendations for the effective use of AID, which was subsequently published in *Endocrine Reviews*.² Here, I will discuss the key highlights of these recommendations, focusing on integration of this technology into clinical practice and adjusting education, training and treatment approaches accordingly.

Indications for AID use

Based on the clinical evidence available at the time of the consensus, the panel advocates that all individuals with T1DM should be considered as potential users of AID systems. A strong level of evidence supports the effectiveness of AID in school-aged children, adolescents and adults. The greatest efficacy was found in adolescents, those who were poorly controlled and those using multiple daily injection therapy³ as their treatment modality. Further studies are needed to investigate AID efficacy in diabetes other than T1DM.

Preparation of the healthcare team

The healthcare team should be equipped with tools to provide competent clinical assessment of AID for routine care, such as the CARES framework.⁴ This framework helps users understand how AID works, how each system calculates insulin delivery, which parameters can be adjusted to optimise settings, when users should revert to an open loop, and critical education points. The healthcare team should also know how to assess glycaemic information and explain CGM data and targets.

Key considerations for starting AID

Before starting AID, the healthcare team should work with the person with diabetes and their family to proactively set realistic expectations for engagement and optimal outcomes. While acknowledging potential burdens, it's important to highlight the benefits that outweigh them. Comprehensive pre-AID education should be provided. It is important to note that AID training should not only focus on technical aspects and, therefore, cannot be separated from education in overall diabetes management. Instead, it represents the tip of the pyramid of diabetes education, where the base represents core diabetes knowledge and management, with CGM and basic pump education in between. Providing adjusted clinical recommendations for AID use maximises system effectiveness, and includes user-initiated bolus for meals, exercise management, treatment of hypoglycaemic and hyperglycaemic events, and effective sick day management.²

Initial device training can be conducted in the clinic, virtually or both, with an individually tailored approach based on current therapy and personal/family skills. Populations with long-standing diabetes and/or suboptimal control require special attention, as they may experience transient worsening of retinopathy and potential microvascular complications following the transition.

Before initiating AID, new CGM users should wear the device for a few days, and those new to a pump may use both devices for 1–2 weeks, to enable recognition of infusion set failures and diabetic ketoacidosis management. Each AID system has slightly different requirements for starting the system and for optimal settings such as glucose targets, active insulin time, insulin to carbohydrate ratio and other modifiable pump settings. Identifying and optimising these settings with healthcare providers can help maximise the benefits of AID education.

Key considerations for follow-up

Access to clinical and technical support is crucial during the early stages of transition to an AID system. As users adapt to the device, the frequency of visits or contacts with the healthcare team can be reduced on an individual basis, while continuing to optimise device settings as needed. The panel also advocates for a standardised AID data report based on the recommended CGM metrics⁵ and glycaemic targets.⁶ It is important to note that currently there are no different glycaemic targets for AID use. However, these targets may change as technology evolves and should be individualised.

The panel concluded with a statement emphasising the importance of making AID systems accessible to anyone who wants to use them, and highlighted the need to consider patient-reported outcomes in treatment choices. More work is required to improve AID interoperability, data access and usability. Faster insulin may eventually enable fully automated AID, with systems serving as a bridge until we have a cure for T1DM.

Revital Nimri

National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

References

1. Abraham et al. 2021 *JAMA Pediatrics* **175** 1227–1235.
2. Phillip, Nimri et al. 2023 *Endocrine Reviews* **44** 254–280.
3. Forlenza et al. 2021 *Diabetes Technology & Therapeutics* **23** 760–762.
4. Messer et al. 2019 *Diabetes Technology & Therapeutics* **21** 462–469.
5. Danne et al. 2017 *Diabetes Care* **40** 1631–1640.
6. Battelino et al. 2019 *Diabetes Care* **42** 1593–1603.

You can read the recommendations in full at <https://doi.org/10.1210/edrev/bnac022>

Pancreatic transplantation in paediatric type 1 diabetes

IPS Kochar summarises the current status of pancreatic transplantation as a management option.

Type 1 diabetes mellitus (T1DM) is an autoimmune-mediated destruction of pancreatic islets, resulting in deficiency of insulin, with acute complications such as hyperglycaemia, ketoacidosis and hypoglycaemia. It is one of the most common paediatric endocrine diseases.

According to the International Diabetes Federation Diabetes Atlas (www.diabetesatlas.org), in 2022, 8.75 million people were living with T1DM globally, of whom 1.52 million were under the age of 20 years. The highest prevalence of T1DM in children and adolescents (individuals <20 years of age) is in India.¹

The associated complications of T1DM put people with the disease at higher risk of mortality than those without T1DM. In children, the causes of mortality are predominantly acute complications. In adults, chronic complications are more often the cause.²

Mortality rates among children with T1DM are declining, due to timely diagnosis, improved management, newer insulin analogues and advances in insulin delivery systems (continuous subcutaneous insulin infusion; CSII).

Currently, the treatments for T1DM are exogenous insulin therapy, basal bolus therapy or CSII. Pancreatic transplantation aims to restore the physiological insulin-secreting capacity of the body and thereby do away with the need for exogenous insulin, if successful. It was first performed in 1966 and >80 000 procedures have been undertaken worldwide (for both T1DM and T2DM).³

Indications and approaches

Indications for transplantation include:

- T1DM of >5 years' duration with negative C-peptide (fasting and/or stimulated)
- glycaemic lability/variability, unawareness of hypoglycaemia
- association with one or more significant chronic diabetes complications, despite compliance with intensive insulin therapy
- post-pancreatectomy or chronic pancreatitis
- cystic fibrosis-related diabetes.

The approaches can be summarised as follows:

- it can be performed as a whole pancreatic transplant, singly or along with another organ, in the form of:
 - simultaneous pancreas–kidney transplant (SPK)
 - pancreas after kidney transplant (PAK)
 - pancreas transplant alone (PTA).
- Isolated islet cell transplantation is also developing as an option.

Whole pancreatic transplantation constitutes major surgery, but may result in longer duration of exogenous insulin independence. In contrast, islet cell transplants are less invasive but may have a shorter duration of sustained outcome.

Pancreases are harvested from brain-dead patients, preferably between 20 and 50 years of age, with a glycated

haemoglobin level <6.5%. The β cell mass required for metabolically significant results after transplantation is recommended to be greater than about 5000 islet equivalents per kg of the recipient body weight.⁴

Complications

Pancreatic transplantation is associated with short term complications, such as graft rejection, hepatic vein thrombosis and hepatic microsteatosis. The patient requiring pancreatic transplantation needs long term immunosuppression and adjunctive peri-transplant anti-inflammatory management, which are associated with considerable side effects of their own. Malignancies following chronic immunosuppression have been reported. The rate of death associated with islet transplantation is very low.

Limitations

- The availability of human pancreases is very low, as they need to be from brain-dead individuals or subjects who have recently died.
- It is major surgery and very expensive.
- Very few centres have the facilities and expertise to undertake the surgery in children with T1DM.
- There are technical hurdles, including issues related to donor, recipient, and graft rejection.
- Studies in children are very limited.

Outcomes

After transplantation, the mimicking of near-normal basal insulin secretion, improved glycaemic control, reduction in episodes of hypoglycaemia, slowing or prevention of secondary complications and reduced dietary restriction are commonly reported. Centres performing pancreatic transplantation have reported maximum benefits approaching 50–70% insulin independence up to 5 years post-transplantation. The maximum duration reported was 10 years following whole pancreas transplantation.⁵

Technological advances in procedures

Areas of investigation include:

- the use of porcine islet cells
- development of pluripotent stem cell-derived islets
- the encapsulation of islets within a protective layer
- techniques to enhance the survival of the graft.

Conclusion

Pancreatic transplantation may have the potential to be a first-line treatment modality, if the associated complications can be reduced.

Many experiments in islet transplantation provide normalisation of glycated haemoglobin with insulin independence. Its lower surgical risk, reduced toxicity from immune therapy and fewer complications make it an ideal future prospect for treatment.

More studies following up transplant procedure are needed before it can be recommended as a routine therapeutic option for T1DM.

IPS Kochar

Kochar Endocrine Clinic, Noida, Uttar Pradesh, India

References

1. Gregory et al. 2022 *Lancet Diabetes & Endocrinology* **10** 741–760.
2. Ruiz et al. 2022 *Diabetologia* **65** 964–972.
3. Boggi et al. 2022 *Transplantation* **106** 147–157.
4. Shapiro 2012 *Review of Diabetic Studies* **9** 385–406.
5. Kochar & Jain 2021 *Annals of Pediatric Endocrinology & Metabolism* **26** 86–91.



IPS Kochar



Pancreatic transplantation was first performed in 1966 and >80 000 procedures have been undertaken worldwide

A new stem cell model to study sex determination

Anu Bashamboo and Ken McElreavey outline the development of a new stem cell model to study sex determination in humans, and associated pathologies.



Anu Bashamboo

Work at the Institut Pasteur (France), together with that of Robin Lovell-Badge at the Francis Crick Institute (UK) and Nitzan Gonen at Bar-Ilan University (Israel), has developed a new stem cell model that allows us to observe the earliest stages of sex determination in humans.¹ This could help us understand the basic mechanism of sex determination and why some people are born with disorders/differences of sex development (DSD), as well as providing a platform for the development of future fertility treatments.

Challenges in understanding

Sex determination and early gonad formation in the human are controlled by poorly characterised gene regulatory networks. Defining and characterising these genetic networks is challenging, since the genes involved in the process are often not conserved in evolution. There are several examples where human genes that cause DSD do not show a phenotype in mouse models.^{2,3}

Furthermore, early developing gonad tissue is difficult to access in the human, and primary gonadal cell cultures lose their cellular identity and do not reflect the *in vivo* gonadal tissue.⁴ One major bottleneck in the field is the lack of a robust *in vitro* model accurately recapitulating *in vivo* development, which can also be used to model genetic variants that cause DSD.

Developing the model

To develop a model of early gonad development, we used induced pluripotent stem cells, which can be directed to become any cell type in the body.¹ From these cells, we developed a robust protocol for sequential differentiation of human induced pluripotent stem cells towards gonadal progenitors using only defined culture medium.

“The new model now allows researchers to study the roles of a range of different genes thought to be involved in sex determination, gonad development and associated pathologies”

Anu Bashamboo received the 2019 Henning Andersen Award in basic research for this work. This research was partially funded by the ESPE Research Unit. Find out about ESPE grants and awards at www.europe.org/grants-awards

Using this system, Sertoli-like cells were derived from healthy 46,XY cells, which showed sustained expression of testis-specific genes, secreted anti-Müllerian hormone and could migrate and then spontaneously aggregate to form 3D tubular structures. When the protocol was used on 46,XX cells, these cells failed to display the characteristics of Sertoli-like cells but instead expressed granulosa markers. This indicates that the differentiation process to Sertoli-like cells requires the presence of the Y chromosome and may recapitulate human testis determination *in vitro*.

This is supported by the observation that, for the first time, this protocol was successfully used to model a naturally occurring pathogenic variant in the *NR5A1* gene which is known to cause 46,XY gonadal dysgenesis. These mutated cells showed aberrant gene expression, failed to migrate and did not spontaneously aggregate to form 3D tubular structures. However, when the *NR5A1* missense variant was corrected by gene editing, the wild type Sertoli-like phenotype was restored.

Implications for future work

In recent years, the Pasteur team has identified several new genes associated with errors in human sex determination, as well as expanding the phenotypic spectrum associated with genes known to cause DSD,^{5,6} but we lacked a suitable biological model to study precisely how these genes cause DSD.

Combined with genome-editing techniques, the new model now allows researchers to study the roles of a range of different genes thought to be involved in sex determination, gonad development and associated pathologies, including DSD and infertility. This discovery could not only help uncover the mechanisms involved

in DSD, but this new model could be used as a platform for spermatogenesis, leading to the development of future fertility treatments.

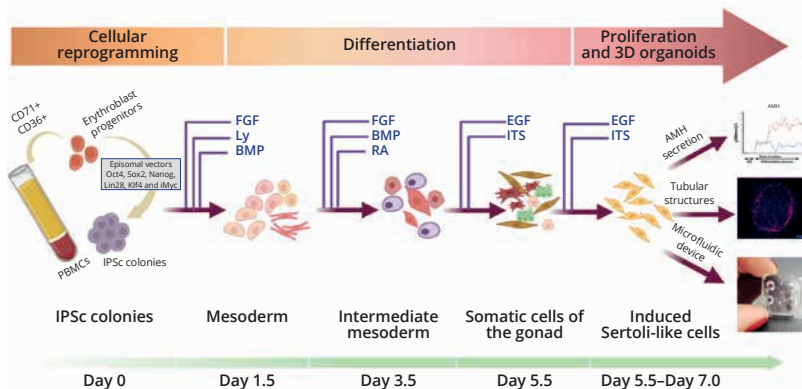


Figure. *In vitro* system of cellular reprogramming recapitulating the *in vivo* development of somatic cells of the human gonad. The reprogramming is independent of targeting exogenous transcription factors. Only by using defined medium are the human pluripotent cells directed to develop towards mesoderm, then intermediate mesoderm that forms cells resembling the fetal Sertoli cells. The *in vitro* derived Sertoli-like cells show sustained expression of testis-specific genes, secrete anti-Müllerian hormone, and can migrate and spontaneously aggregate to form 3D tubular structures. The systematic formation of these testicular organoids is visualised using a specially designed microfluidic device. IPSC, induced pluripotent stem cells; PBMCs, peripheral blood mononuclear cells.

Anu Bashamboo & Ken McElreavey
Institut Pasteur, Paris, France

References

- Gonen et al. 2023 *Science Advances* **9** eabn9793.
- Bashamboo et al. 2016 *Human Molecular Genetics* **25** 5286.
- Bashamboo et al. 2018 *American Journal of Human Genetics* **102** 487–493.
- Beverdam et al. 2003 *Cytogenetic Genome Research* **101** 242–249.
- McElreavey et al. 2020 *Genetic Medicine* **22** 150–159.
- Harris et al. 2018 *Proceedings of the National Academy of Sciences of the USA* **115** 5474–5479.



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21–23 September 2023
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- **The role of the food environment in the global childhood obesity epidemic** Frank Hu (USA)
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Eveline Crone (The Netherlands)
- **How AI will change medicine**
Henk Marquering (The Netherlands)
- **Stem cells, organoids and single cell transcriptomics** Hugo Vankelecom (Belgium)
- **How the genome predicts human disease**
Stylianos Antonarakis (Switzerland)
- **Novel approaches in autoimmune endocrine disorders** Olle Kämpe (Sweden)
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Hans de Vries (The Netherlands)

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ESPE e-Learning

Answer to the case query on [page 5](#)

Features indicating that this could be a family with MODY

The autosomal dominant family history of diabetes
The neonatal hypoglycaemia
The macrosomia at birth

Macrosomia (birth weight >4kg) is a feature of *HNF4A* MODY, and is seen in >50% of cases, with birth weight increased by an average of 790g compared

with unaffected siblings. Birth weight is increased whether the mother or father has *HNF4A* MODY.

Neonatal hypoglycaemia requiring treatment is seen in around 15% of cases where the baby has inherited the *HNF4A* mutation from their affected parent. This hypoglycaemia typically remits during infancy and patients develop diabetes from adolescence.

The autosomal dominant family history is a key feature of *HNF4A* MODY. Each child has a 50% chance of inheriting the *HNF4A* mutation. The HbA1c is not helpful in identifying *HNF4A* MODY.

ESPE

European Society for
Paediatric Endocrinology

Improving care of children with
endocrine diseases by promoting
knowledge and research

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ESPE Newsletter

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