MANCHESTER 1824
The University of Manchester

The University of Manchester Research

A new era in obesity management

DOI:
https://doi.org/10.6084/m9.figshare.20152499

Document Version
Final published version

Link to publication record in Manchester Research Explorer

Citation for published version (APA):
Syed, A. (2022). A new era in obesity management. *The Endocrinologist*, (144), 7-8. https://doi.org/10.6084/m9.figshare.20152499

Published in:
The Endocrinologist

Citing this paper
Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights
Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy
If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [http://man.ac.uk/04Y6Bo] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.

OPEN ACCESS

Download date:30. Jun. 2022

Additionally, regional organisational and service delivery barriers can further restrict the widespread use in an eligible population.

WHAT THE FUTURE HOLDS

The landscape of technology in type 1 diabetes care is changing at an unprecedented pace. More sophisticated commercial systems are being developed by industry and being rolled out early as a result of the success seen in recent years.

Radical changes to the NICE eligibility criteria in 2022 will result in wider availability of CGM to all individuals with type 1 diabetes. The ongoing real world HCL trial in England will further shed light on its effectiveness across children, young people and adults, with results expected towards the end of 2022.

FURTHER READING

1. Wilmot EG *et al.* 2021 *Diabetic Medicine* **38** e14433.
2. Battelino T *et al.* 2019 *Diabetes Care* **42** 1593–1603.
3. Messer LH *et al.* 2019 *Diabetes Technology & Therapeutics* **21** 462–469.
4. Ng SM & Evans ML 2021 *Diabetic Medicine* **38** e14620.

The aim to reduce inequalities in uptake remains at the forefront of current policy and transformational plans within NHS England. However, individualised care, support and education, with clinical leadership, remain the most powerful drivers, as always, in adoption of 'game-changing' technology within type 1 diabetes care in the NHS.

REZA ZAIDI
Consultant Diabetologist, Liverpool University Hospitals NHS Foundation Trust; Children & Young People's (CYP) Diabetes Oversight Group, NHS England

FULYA MEHTA
Consultant Paediatric Diabetologist, Alder Hey Children's Hospital, Liverpool; National Clinical Lead – CYP Diabetes, NHS England

PARTHA KAR
Consultant Diabetologist, Portsmouth Hospitals NHS Foundation Trust; National Specialty Advisor, NHS England

A NEW ERA IN OBESITY MANAGEMENT

WRITTEN BY AKHEEL SYED

Obesity is not a new phenomenon, it's as old as humanity itself. The Venus of Willendorf (Vienna, Austria) stands testimony to the recognition, and perhaps celebration, of (pathological) voluptuousness in the Palaeolithic era (pictured on page 8).

What is new, however, is the unimaginable scale of the obesity epidemic today. The World Health Organization estimates that, as of 2016, over 650 million adults (13%) globally had clinical obesity. The situation is worse in Western countries: 28% of adults in England and 42% in the USA have obesity.

HOW DID WE GET HERE?

It's complicated! The situation is the result of a perfect storm of evolutionary biology adapted for energy conservation, honed by genetic selection through millennia of food insecurity, laid low by the fruits of the industrial revolution.

A dawning realisation of the strong biological underpinnings of obesity as a 'disease', not a 'lack of moral fibre' (as has often been stigmatisingly made out in popular culture), has come from advances in our understanding of genetic and epigenetic influences, the interplay of complex endocrine pathways, the gut microbiome, and our interaction with the built environment. The Foresight report, *Tackling Obesities*, identified a huge range of factors that influence obesity in broad clusters of physiology, individual psychology, individual activity, physical environment, societal influences, food production and food consumption.[1]

HISTORICAL MANAGEMENT

In the face of such complexity, the management of obesity has often been an overly simplistic 'a calorie in, a calorie out' mantra. Galen of Pergamon, sharing his tips two millennia ago, declared, "I reduced a huge fat fellow to a moderate size in a short time, by making him run every morning until he fell into a profuse sweat; I then had him rubbed hard, and put into a warm bath; after which I ordered him a small breakfast, and sent him to the warm bath a second time. Some hours after, I permitted him to eat freely of food, which afforded but little nourishment; and lastly, set him to some work which he was accustomed to for the remaining part of the day."

So, how far have we come since Galen? The DiRECT study has shown the efficacy of lifestyle and dietary changes for weight loss and diabetes remission for up to two years in people with type 2 diabetes.[2] However, the success of non-drug weight management on a long term epidemiological scale is rarely lasting.

The pursuit of effective adjunctive weight loss medications has come a long way since DNP (2,4-dinitrophenol) in the 1930s, which induced

'Whilst many more agents are on the horizon, the holy grail of a single common target for the treatment of "idiopathic" obesity may instead prove to be a multilevel, multichannel product incorporating several molecules.'

thermogenesis by uncoupling of oxidative phosphorylation – literally a 'fat burner' that caused death by hyperthermia! The past couple of decades have seen the marketing and subsequent withdrawal of weight loss products such as rimonabant (psychiatric adverse effects) and sibutramine (cardiovascular events). Thus, orlistat was the only licensed medicinal product for weight loss in the UK/EU for much of the 2010s.

THE DAWN OF A NEW ERA

It is now the dawn of a new era of medical therapies for obesity. Many have cut their proverbial teeth in the treatment of type 2 diabetes. Whilst all agents from the glucagon-like peptide 1 (GLP1) receptor agonist class have proved their weight loss benefits, two products – liraglutide and semaglutide – now have marketing authorisation for a weight loss indication.

From the early days of recombinant leptin therapy in congenital leptin deficiency,[3] targeted drug discovery for single gene disorders has brought the promise of effective weight loss therapy for pro-opiomelanocortin, proprotein subtilisin/kexin type 1 and leptin receptor deficiency syndromes, with the first-in-class melanocortin-4 receptor agonist setmelanotide[4–6] approved for use in 2020–2021.

Whilst many more agents are on the horizon, the holy grail of a single common target for the treatment of 'idiopathic' obesity may instead prove to be a multilevel, multichannel product incorporating several molecules. We are already seeing that with some novel products in development, such as GLP1–glucagon, glucose-dependent insulinotropic polypeptide (GIP)–GLP1 and amylin–calcitonin dual agonists, and GIP–GLP1–glucagon tri-agonists.[7] Some are approaching an efficacy similar to that of bariatric surgery.

SURGICAL APPROACHES

Bariatric surgery itself has come a long way since the 10th century when, it is claimed, King Sancho I of León (Spain), nicknamed Sancho the Fat, underwent suturing of his lips to restrict him to a liquid diet through a straw. He is said to have lost half his weight, to return triumphant to regain his throne.[8]

Bariatric surgery has rapidly evolved from the jejuno–ileal bypass of the 1950s to modern day laparoscopic techniques. Whilst minimally invasive endoscopic techniques are continually being developed, sleeve gastrectomy and gastric bypass have stood the test of time for weight reduction, remission or amelioration of weight-related co-morbidities, and improvement in life expectancy,[9] earning the epithet 'metabolic surgery'. It didn't take long for bariatric surgeons to troll diabetologists with the assertion, "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus."[10]

An exciting fallout from bariatric surgery is its effect on cancer risk. Cancer Research UK's adverts of a few years ago, highlighting that obesity has overtaken smoking as the leading cause of bowel, kidney, ovarian and liver cancers, may have been derided as scaremongering. However, the significantly increased risk of several cancers in people with obesity is undeniable.

Endometrial cancer is a case in point. The fourth most common cancer of women in the UK, its risk is increased by 50% for every 5kg/m^2 excess body mass index. Our group has shown that significant weight loss (by bariatric surgery or lifestyle and dietary management) can reverse endometrial precancerous changes.[11,12]

Similarly, the risks of obesity and the benefits of weight loss are increasingly recognised in women with infertility and patients awaiting organ transplantation. We now have local pathways for intensive weight management and/or expedited bariatric surgery for such patients.

Venus of Willendorf, a female Palaeolithic limestone figurine tinted with red ochre. ©Naturhistorisches Museum, Vienna/Steven Zucker (reproduced under CC BY-NC-SA 2.0 licence; https://creativecommons.org/licenses/by-nc-sa/2.0)

We are on the cusp of a revolution in medical therapies for obesity, but cost-effectiveness remains a hindrance until drug pricing becomes affordable. Until such time, bariatric surgery remains the most clinically effective and cost-effective treatment there is for severe obesity.[13]

AKHEEL SYED
Consultant Endocrinologist, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, and Faculty of Biology, Medicine and Health, University of Manchester

REFERENCES

1. Butland B *et al.* 2007 *Tackling Obesities: Future Choices,* edn 2. London: Government Office for Science.
2. Lean MEJ *et al.* 2019 *Lancet Diabetes & Endocrinology* **7** 344–355.
3. Farooqi IS *et al.* 1999 *New England Journal of Medicine* **341** 879–884.
4. Clement K *et al.* 2018 *Nature Medicine* **24** 551–555.
5. Clement K *et al.* 2020 *Lancet Diabetes & Endocrinology* **8** 960–970.
6. Kühnen P *et al.* 2016 *New England Journal of Medicine* **375** 240–246.
7. Müller TD *et al.* 2022 *Nature Reviews Drug Discovery* **21** 201–223.
8. Faria GR 2017 *Porto Biomedical Journal* **2** 90–92.
9. Carlsson LMS *et al.* 2020 *New England Journal of Medicine* **383** 1535–1543.
10. Pories WJ *et al.* 1995 *Annals of Surgery* **222** 339–350.
11. MacKintosh ML *et al.* 2019 *International Journal of Cancer* **144** 641–650.
12. Barr CE *et al.* 2021 *Cancer Prevention Research* **14** 1041–1050.
13. Boyers D *et al.* 2021 *International Journal of Obesity* **45** 2179–2190.