EndoCompass Project: Diabetes and Obesity Topic Area

Table of Contents

Subtopic 1: Underlying mechanisms of obesity and Type 2 Diabetes, including monogenic forms – WG1

Monogenic diabetes

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Monogenic diabetes, caused by single-gene mutations, represents between 1-4% of all diabetes cases in infants and young adults. It is still underdiagnosed and patients are often misidentified as T1D or T2D, hindering appropriate therapeutic management and worsening their prognosis. Future improvements in monogenic diabetes require a focused research approach encompassing different aspects:

a. Better Awareness and diagnosis

Limited awareness among healthcare providers about monogenic diabetes significantly hinders accurate diagnosis. This challenge is exacerbated by the overlapping clinical features with T1D and T2D, along with the diverse clinical presentations seen in patients with monogenic diabetes. Improvements in awareness and testing methods are steadily leading to an increase in the diagnosis rate in the last decade (PMID: 35061023). The creation of a pan-European monogenic diabetes registry combining the information from the multiple existing national registries would greatly increase knowledge about prevalence, allow better clinical diagnosis, and facilitate possible clinical trials. A consensus report from the ADA/EASD Precision Diabetes Medicine Initiative provided recommendations on who and how to test for monogenic diabetes (PMID: 37794142) and identified open research challenges such as the urgent need for sequencing data in monogenic diabetes genes from diverse populations.

b. Basic and Translational Research

Research priorities include advancing knowledge of disease pathogenesis and heterogeneity through the molecular characterization of genes associated with monogenic diabetes, most of which affect pancreas development and/or β-cell function. Since mouse models often fail to replicate human phenotypes accurately, the use of human pluripotent stem cells to model pancreas development and survey β-cell function is an invaluable tool for characterizing the effects of human variants. Research along these lines might help to identify effective therapies tailored to individual genetic profiles (PMID: 35008927). While there are ongoing clinical trials exploring the use of insulin producing cells derived from stem cells in T1D, the immune system is not involved in most monogenic diabetes. Thus, initial clinical tests in some rare forms of diabetes, such as neonatal diabetes, might be more suitable and easier to optimize (PMID: 30503261).

Genetics and epigenetics of obesity and type 2 diabetes

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Current state-of-the art

Comprehensive genomic testing is on its way to change modern medicine.
Obesity is complex and arises from the interaction of social factors, the environment and genetic factors. Based on family studies, twin studies and adoption studies, estimated BMI heritability can reach 40-70%. Over 1,000 variants of gene loci, including single nucleotide polymorphisms (SNPs), are significantly associated with obesity. Obesity is a condition with excess body fat which develops after birth and is mainly driven by a dysregulation of hunger/energy intake and energy expenditure. Genes regulate weight across the whole spectrum. Especially early-onset, severe obesity is strongly driven by genetic factors. Genetic discoveries in mice and in humans identified leptin and the leptin - MC4R pathway that regulates body weight.
Recent findings show a complex central nervous system involved in the regulation of energy balance. Rare variants in genes involved in this system may cause rare monogenic obesity. The combination of several common risk variants (SNPs) increase the risk for the development of common obesity.
Epigenome-wide analyses demonstrate the correlation of DNA methylation with clinical features of obesity (PMID: 30399374). Candidate gene studies provided evidence for the involvement of DNA methylation in obesity, for example altered DNA methylation at genes that code for adipokines and influence hunger and satiety (PMID: 25929254; PMID: 27568547).
Moreover, epigenetic modifications can mediate the influence of environmental factors on gene expression and phenotype. Age, diet, physical activity, environment and pollutants, and disease status may influence cell and tissue-specific epigenetic modifications of DNA. Some mechanisms of epigenetic genome modifications are already known as the cause of obesity. Epigenome-wide analyses demonstrate the correlation of DNA methylation with clinical features of obesity (PMID: 30399374). Candidate gene studies provided evidence for the involvement of DNA methylation in obesity, for example, altered DNA methylation at genes that code for adipokines and influence hunger and satiety (PMID: 25929254; PMID: 27568547). However, further epigenetic modifications can be involved as risk factors in the development of obesity (for ex., posttranslational modification of histone proteins and non-coding RNA-associated gene silencing). Additionally, there is evidence of intergenerational epigenetic inheritance in humans regarding obesity and T2D (PMID: 30982733) and for a paternal impact on offspring epigenetic modifications. Relevant evidence raises regarding the genetic imprinting on the fetus and in the first years of life related to the development of obesity (DOI 10.1007/s11154-023-09804-6). Knowledge about epigenetic mechanisms related to obesity and T2D could be the key to developing strategies to prevent and treat diseases.

Research priorities

There is a significant number of (1) patients with obesity suspicious for a genetic or epigenetic cause but unknown gene variant or epigenetic variation, (2) patients with a genetic diagnosis but unknown mechanism of disease, and (3) patients suffering from defined rare form of obesity with limited understanding of pathogenesis and/or limited therapeutic options.

In order to resolve these gaps it will be necessary to (1) establish a diagnostic pipeline employing whole genome sequencing (WGS) including non-coding genome and epigenome and innovative bioinformatics tools to improve efficacy of genetic diagnosis for rare diseases, (2) elucidate molecular pathomechanism and define key drivers/pathways of disease by complementing genomics with innovative multi-omics integration including single cell transcriptomics, proteomics, metabolomics, and epigenetics, (3) validate identified targets in state of-the-art patient-derived disease models (iPSC- or primary cell-based 2D and 3D models) and animal models.

In cases where traditional genetic testing fails to pinpoint pathogenic mutations, DNA methylation arrays might offer an alternative avenue in the diagnosis of monogenic obesity. These arrays identify specific epigenetic signatures associated with monogenic. Understanding these patterns can shed light on how gene expression is regulated in individuals with genetic mutations, providing valuable insights into the molecular mechanisms underlying the condition. The identification of monogenetic

obesity-specific genome-wide DNAm alterations will facilitate both the elucidation of the molecular pathophysiology and the development of improved diagnostic testing.

The genetic causes of obesity create a spectrum of disorders - starting from a pathogenic mutation that will result in severe early-onset obesity in all mutation carriers, through monoallelic mutations giving incomplete penetrance (e.g. in *MC4R*) to polymorphisms that only slightly affect body weight. However, even in patients with the same mutations, different phenotypes can be observed - regarding body weight and other clinical symptoms. Explaining this variability may be crucial. In some patients, such variability theoretically could result from additional molecular abnormalities (mutations in other genes, changes in the non-coding region, epigenetic modifications, etc.). Examples include siblings with BBS syndrome with a divergent phenotype or monozygotic twins, of which only one developed ROHHAD features (PMID: 21807698.

Currently, mutations in over 120 genes are known to be related to monogenic obesity. Some mutations are confirmed to be pathogenic based on functional studies. However, the development of genetic testing techniques (NGS) has made it possible to detect many genome changes (within the coding and non-coding regions) whose clinical significance is unknown (VUS). The development of collaborative consortiums addressing existing clinical evidence and even performing functional analysis of VUSs could allow for their reclassification resulting in more accurate diagnosis and patient treatments (i.e. PMID: 37898381). There is a need to develop databases into which variants detected in genes that could be related to obesity could be introduced, as well as related tools and software using AI and machine learning to improve the theoretical analysis of discovered changes. Looking at the most common cause of monogenic obesity related to mutations in the *MC4R* gene, for which a dedicated website was created collecting all helpful information (https://www.mc4r.org.uk/), worth considering it seems to be taking similar initiatives concerning other genes related to obesity. Establishing a registry for patients with monogenic obesity and creating research networks and websites dedicated to particular genes can be useful for both researchers and clinicians. Thereby the list of genes potentially involved in monogenic obesity over those already known (mainly in the LEP-MC4R pathway and in dysmorphic syndromes) can be expanded by comparative WES analysis of patients with singularly severe or particular forms of obesity. It can be used to exchange knowledge and develop new strategies for future research and patient care.

Additionally, there is a clear need to improve treatment strategies. Individuals with different genetic/ epigenetic risk profiles might react differently to treatment strategies (e.g. conservative multi-professional counselling, bariatric surgery, pharmacological treatment). Therefore, increased knowledge of responsiveness to treatment options in combination with detailed information about genetic/ epigenetic signatures will allow to select the best individual treatment combination.

Anticipated impact of future research

Understanding the genetic / epigenetic and pathophysiological cause of rare genetic forms of obesity will pave the way for our understanding of common forms of obesity (‘Rare to Common’). Identifying pathways and molecules involved in the regulation of hunger and body fat mass in more detail will be the basis for the development of mechanism-based pharmacological interventions. It will also be the basis for future screening programs opening the way for early prevention of gaining excess body fat.

Subtopic: Brain-periphery communication

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Current state-of-the art

Obesity is characterized by disturbed energy homeostasis resulting from impaired regulation affecting the crosstalk of several organs. Brain-periphery communication receives growing attention in understanding the pathophysiology of obesity and T2D. The brain's role in appetite regulation involves multiple regions that influence attentional focus, reward processing, and motivational aspects of food consumption. The central nervous system, especially the hypothalamus, integrates signals from peripheral tissues such as adipose tissue, the liver, immune system, and the gut. These signals are mainly transmitted by hormonal pathways (e.g., GLP-1, ghrelin, leptin, insulin) and neural (vagal) routes to the brain. In particular, the gut-brain axis is emerging as a central regulator of energy balance, appetite, and metabolism (DOI: 10.1016/s0016-5085(98)70540-2). Dysregulation within these intricate networks can lead to impaired appetite control, overeating, and disruptions in energy homeostasis, contributing to obesity and metabolic disorders like T2D.

Leptin and Ghrelin

Leptin, secreted by adipocytes, represents a key hormone in brain-periphery communication. It suppresses appetite and stimulates energy expenditure mainly via proopiomelanocortin (POMC)-expressing neurons in the hypothalamic arcuate nucleus (DOI: 10.1523/JNEUROSCI.23-18-07143.2003, DOI: 10.1097/PSY.0b013e31821a196f). Obesity is associated with evolving insulin and leptin-resistance, not only in the periphery but also in the central nervous system. Ghrelin is an example of an orexigenic gut hormone that is predominantly synthesized in enteroendocrine cells of the stomach, stimulating food intake by activation of agouti-related peptide (AgRP) and neuropeptide Y (NPY)-producing neurons in the arcuate nucleus, while also acting peripherally via afferent vagal activity (DOI: 10.1016/j.molmet.2021.101175).

Enteroendocrine cells

Enteroendocrine cells (EECs), though only accounting for 1% of gastrointestinal epithelial cells, make the gut the largest endocrine organ (DOI: 10.1016/j.molmet.2021.101175). ECCs in the distal intestine secrete anorectic hormones, such as glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), peptide YY (PYY), and cholecystokinin (CCK). These hormones contribute to the gut-brain communication by transmitting signals about the nutritional status to the brain, affecting energy balance, appetite and reward system (DOI: 10.2220/biomedres.41.199, DOI: 10.1016/j.molmet.2021.101175, DOI: 10.1152/physrev.00018.2018, DOI: 10.3389/fnins.2013.00181, DOI: 10.3389/fendo.2014.00058, DOI: 10.1016/j.mce.2015.02.017).

Gut Microbiota

The gut microbiome has been identified as an important factor in obesity (DOI: 10.2220/biomedres.41.199, DOI: 10.1111/jne.12684). Some gut bacteria have been identified to modify hypothalamic neuroendocrine pathways by affecting the secretion of gut hormones (including GLP-1, ghrelin, and PYY), fostering the new concept of a microbiota-gut-brain axis. This has been underlined by transplanting gut bacteria from obese into lean mice, inducing greater weight gain than bacteria from lean mice (DOI: 10.1016/j.chom.2008.02.015).

Neural Pathways and Brain Regions

The vagus nerve serves as a crucial link between the gut and the brain, mainly the hypothalamus (DOI: 10.1053/j.gastro.2016.10.046, DOI: 10.1152/physrev.00018.2018, DOI: 10.1016/j.neuropharm.2011.10.008). The arcuate nucleus, plays a critical role in regulating energy and glucose homeostasis by integrating signals from peripheral hormones to manage calorie intake, glucose metabolism, and energy expenditure (DOI: 10.1038/nature11705). Within the arcuate

nucleus, proopiomelanocortin (POMC) neurons inhibit feeding, while agouti-related peptide (AgRP) neurons promote hunger. These neurons project to other hypothalamic regions, including the paraventricular nucleus, lateral hypothalamus, and ventromedial nucleus, which further integrate signals to control food intake and energy expenditure.

Research priorities

Leptin and Ghrelin dysregulation

In obesity, the leptin and ghrelin dysregulation- characterized by leptin resistance and elevated ghrelin levels—contributes to excessive caloric intake, weight gain, and metabolic dysfunction, further promoting the development of metabolic syndrome and T2D (DOI: 10.1530/JOE-15-0139, DOI: 10.1038/ncpendmet0196). Further research that targets the molecular mechanisms behind leptin and ghrelin dysregulation, particularly within the central nervous system, is crucial for developing effective therapeutic strategies for obesity and T2D. Research into the specific brain regions interacting with leptin, ghrelin and hunger signaling will enhance our understanding of how leptin and ghrelin dysregulation contributes to obesity and metabolic complications. Also, more research on potential targeted treatment options in the context of leptin/ghrelin is needed.

Enteroendocrine cells as therapeutic targets

Targeting EECs and their hormones has become a focus for therapeutic strategies in obesity and T2D (DOI: 10.1016/j.molmet.2021.101175, DOI: 10.1152/physrev.00018.2018, DOI: 10.1016/j.molmet.2021.101175). Further research in exploring EEC signaling dynamics and how different nutrients and metabolic states, such as fasting or caloric restriction, influence hormone secretion from EECs is needed. Understanding how key hormones (like Ghrelin, GLP-1, PYY, and GIP) respond to changes in diet or energy balance will help clarify their role in controlling food intake and energy expenditure. In addition to understanding these dynamics, targeting EEC hormones and their central effects presents an opportunity for therapeutic advancements. Incretin-based treatments, such as GLP-1 receptor agonists, have already shown promise in managing obesity and T2D. Further research into regulating other EEC hormones like PYY and CKK could enhance our ability to treat metabolic diseases.

Gut Microbiota and Hormonal Regulation

Recent focus has been directed to the gut microbiome not only changing with metabolic disorders but also being causally involved (DOI: 10.1152/physrev.00018.2018; DOI: 10.3389/fimmu.2020.604179, DOI: 10.1136/gutjnl-2017-314050). Given the key role of the gut microbiota in the modulating appetite, energy homeostasis and metabolism, it is not unexpected that the microbiota is currently a target for the prevention and treatment of metabolic disorders such as obesity. However, more studies are needed before gut microbiota-based therapy is used as a therapeutic tool to suppress appetite and food intake and restore metabolic imbalances in obesity and other metabolic disorders. Research on understanding how the gut microbiota influences the production and function of key gut hormones such as GLP-1, PYY, and ghrelin is needed. New data on these interactions is needed to uncover how microbiome shifts may drive hormonal imbalances and promote obesity and metabolic disorders. In parallel, microbiome-based therapies offer a promising approach to addressing these issues (DOI: 10.1172/JCI143772, DOI: 10.1111/j.1365-2826.2011.02226.x). Manipulating the gut microbiome—through probiotics, prebiotics, or other interventions—could enhance the effectiveness of hormonal therapies and improve gut-brain communication. Despite identification of specific dietary factors altering the microbiome, they need more intensive investigation to draw clear conclusions and dietary suggestions. There also is increasing attention to the pathobiological importance of short-chain fatty acid generation, which

regulates intestinal physiology, immune function, inflammation and paracrine signaling, and act both directly in the hypothalamus and indirectly by release of the anorectic gut hormones, peptide YY (PYY) and GLP1 (DOI: 10.1111/jne.12684, DOI: 10.3390/ijms221810028, DOI: 10.3390/nu8050281). However, more research is needed in this field. Also, GLP-1 treatment and bariatric surgery have shown to change the gut microbial composition to a profile like that observed in lean (DOI: 10.1089/met.2018.0088, DOI: 10.1007/s11695-017-2595-8, DOI: 10.1016/j.chom.2008.02.015), offering a potential target for further research on how the microbiota not only affects obesity but also is affected by different treatment options.

Neural Pathways and Brain Regions

Further research priorities could include investigating the specific mechanisms by which POMC and AgRP neurons influence the activity of their downstream targets. Exploring how alterations in the melanocortin pathway contribute to obesity and metabolic disorders will be crucial. Studies could also focus on the effects of environmental factors, such as diet and stress, on melanocortin signaling, as well as the potential for therapeutic interventions targeting this pathway to restore energy homeostasis in individuals with obesity. Another key question is how prominent neuronal centers that regulate feeding, such as the hypothalamic nuclei, are influenced by and linked to higher-level brain regions, including the reward system and sensory inputs (such as gustatory and olfactory systems).

Deep phenotyping focusing on neurocognitive functioning (e.g., inhibitory control), interoceptive deficits and food-related brain networks in subsamples (fMRI) will be the basis to obtain insights into etiologic mechanisms as well as into neurocognitive and behavioral markers. It is currently unknown to what extent excess weight is associated with functional alterations in the brain's reward system. In this respect, exploring the reward system is of interest especially early in life during highly active shaping of neuronal connections.

White adipose tissue

The contribution of cellular heterogeneity and architecture to white adipose tissue (WAT) function is poorly understood (PMID: 34380013). By means of combined spatially resolved transcriptional profiling with single-cell RNA sequencing and image analyses it will become possible to map humanWAT adipocyte heterogeneity.

The impact of common metabolic disorders such as type 2 diabetes on WAT microarchitecture and the proportion of different fat cell subtypes needs to be studied. Furthermore, the contribution of adipocyte heterogeneity to insulin resistance and/or ectopic lipid will be a main research field.

Further aspects

The role of omics studies (metabolomics, lipidomics) should be enhanced and could be extended to the study of the pathophysiological bases of T2DM and other obesity associated metabolic comorbidities.

Analyses of big data using artificial intelligence and integration of innovative methodology (e.g. metabolomics, lipidomics) will probably provide more insights into tissue–tissue communication.

The natural history of T2DM development from childhood to adulthood should be studied. This would include the study of the determinants of the onset insulin resistance and "prediabetic" conditions (singularly altered glucose tolerance) and their progression to T2DM, along with the considerations for different profiles among T2DM patients.

Anticipated impact of future research

The anticipated impact of future research on brain-periphery crosstalk and their targeted therapies for obesity and T2D is significant. It will enhance our understanding of how the complex microbiota-gut-brain axis interacts reciprocally, providing insights into appetite regulation, energy expenditure and metabolism. Studies on how genetic, metabolic, and lifestyle factors influence individual responses to gut hormones and their impact on obesity treatment could lead to novel therapeutics, identifying specific targets that may result in enhancing treatment options to improve metabolic health.

In summary, this research holds the potential to transform our understanding and treatment of obesity and T2D, leading to improved health outcomes.

Subtopic: Environmental factors

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Current state-of-the art

Obesity emerges based on an individual predisposition (genetic and epigenetic factors) and the complex interaction with environmental factors. Preconceptual and prenatal period seems to be highly sensitive for epigenetic alterations (prenatal programming of hormonal circuits). Furthermore, psychosocial determinants are key drivers for the physical and mental health status and the quality of life of children and adolescents.

The identification of the prenatal phasis and early childhood as a critical period for manifestation of sustained obesity and ensuing progressive metabolic dysfunction implies that it will be critical to disentangle contributing factors to enable individual risk prediction and to identify mechanisms leading to early metabolic deterioration.

Obesity development is driven by a complex interaction between genetics and environmental factors, and brain's regulation of food intake and energy balance. In addition to traditional risk factors, new risks related to environmental factors have emerged.

Research priorities

Childhood

The major challenge is the complexity of the environmental context, the so-called exposome, comprising a multitude of impacting factors including psychosocial, chemical, geophysical and biological factors, health conditions, and health-related behavior.

Imbalanced responses or maladaptation to changing environmental challenges can impose profound and sustained effects on the developing organism, with particular impact during vulnerable developmental windows. These exposures act simultaneously via distinct and/or shared mechanistic pathways during vulnerable phases of child development such as the pre- and perinatal period.

An overall research aim is to identify biological, psychosocial and behavioral markers of childhood obesity risk. This will be achieved by applying epidemiological approaches closely interlinked with environmental monitoring, molecular profiling, and mechanistic research. Furthermore, pregnancy and birth cohorts with long term follow-up and deep phenotyping including investigation of biomaterial will have the potential to reveal critical exposures.

Based on comprehensive understanding of etiology from the epidemiologic approach, it will be possible to develop risk prediction tools for obesity and for progressive metabolic deterioration. The application of these tools will identify high-risk patients. By this approach it will also be possible to identify protective factors for childhood obesity and metabolic risk.

Dietary Patterns and Nutrition

The rising prevalence of obesity is significantly influenced by various environmental factors related to dietary habits and nutrition (DOI: 10.3390/nu16111629). Increased consumption of high-calorie, processed foods, such as fast food, sugary drinks, and snacks, is prevalent. Also developing countries experience rapid economic transitions that shift dietary patterns from traditional diets to Western-style diets high in fats and sugars.

Additionally, larger portion sizes in restaurants and packaged foods contribute to overeating, while the availability of unhealthy food options further affect dietary choices. Aggressive marketing of high-fat, sugary foods, particularly aimed at children, shapes consumer preferences and eating behaviors.

Research insights into these factors could inform proactive prevention strategies for obesity by promoting dietary patterns that support a healthy metabolism and energy balance. Moreover, the findings could help shape public health policies emphasizing gut health in obesity management, ultimately aiming to reduce the prevalence of metabolic disorders.

Evaluation of and adaptations to Family-based behavioral treatment that specifically address satiety responsiveness as monitored by fMRI will help children and families better implement behavior change and be more successful in treatment (PMID: 32713944).

Behavior and sedentary lifestyles

The prevalence of obesity is exacerbated by reduced physical activity due to various environmental factors (DOI: 10.1186/1479-5868-8-98, DOI: 10.1210/jendso/bvad090). Increasing sedentary behavior is linked to work environments that promote desk jobs and long hours spent in low-activity settings, as well as the widespread use of technology such as computers, smartphones, and television. Additionally, urbanization has led to a reliance on cars and diminished opportunities for walking or cycling, further contributing to decreased physical activity levels. These combined factors result in reduced energy expenditure, significantly impacting obesity rates. Further research is needed to address targeted individual and public health intervention strategies against sedentary lifestyles.

Circadian Disruption

Irregular work hours and night shifts disrupt circadian rhythms, leading to hormonal imbalances that affect appetite regulation and metabolism (DOI: 10.1371/journal.pone.0300074, DOI: 10.3390/nu15102286). This disruption often results in increased cravings for high-calorie foods and difficulty maintaining healthy eating patterns, heightening the risk of obesity and T2D. Investigating how irregular work hours specifically affect hormones involved in appetite regulation, such as ghrelin and leptin, can provide insights into the mechanisms linking shift work to obesity and T2D.

Psychosocial Factors

Chronic stress and emotional eating are significant contributors to the rising prevalence of obesity and T2D (DOI: 10.3390/nu15051173). Ongoing stress affects HPA axis, leading to disrupted cortisol levels and cravings for high-calorie foods (DOI: 10.1146/annurev-psych-010418-102936). Emotional eating, e.g. binge-eating is another important topic where targeted intervention strategies are needed (DOI: 10.3390/ijerph20032722).

Pollution

Air pollution and exposure to endocrine-disrupting chemicals (EDCs) are emerging environmental factors that may contribute to the rising prevalence of obesity and T2D (PMID: 33201649, DOI:

10.3390/ijms24108870). Recent research suggests that exposure to air pollution may be linked to obesity through inflammatory responses and metabolic disruptions. Further investigating how air pollution contributes to inflammatory responses and metabolic changes will provide valuable insights into its role in obesity and T2D.

Endocrine-Disrupting Chemicals (EDCs), such as bisphenol A (BPA) and phthalates, are chemicals commonly found in plastics, personal care products, and food packaging. These substances have shown to interfere with hormonal systems, potentially contributing to obesity by altering metabolism and fat storage (DOI: 10.1038/nrendo.2015.163, DOI: 10.1007/s13679-017-0240-4, DOI: 10.1038/nrendo.2016.186). EDCs may disrupt the normal functioning of hormones involved in appetite regulation and energy balance, exacerbating weight gain and increasing the risk of T2D. Longitudinal studies that track the effects of EDC exposure on body weight, metabolism, and hormonal regulation can help establish causal relationships and identify vulnerable populations.

Anticipated impact of future research

Future studies will be crucial for identifying effective public health strategies aimed at mitigating the environmental factors for obesity and T2D. Insights into how socio-economic factors and their biological effects influence eating behaviors and energy expenditure are essential to develop targeted interventions that promote healthier lifestyles and dietary habits.This holistic approach to understand and prevent obesity and T2D is essential for developing comprehensive strategies that not only address individual behaviors but also reshape the environments that contribute to these widespread health issues.

Subtopic 2: Disease Modifying therapies in obesity and Type 2 Diabetes – WG2

Future perspectives in obesity pharmacotherapy

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Current state of the art

Obesity is recognised as a chronic disease and a major global health challenge [1]. For a long time, pharmacological treatments have been limited by low efficacy; older drugs like Orlistat result in a -2.9% placebo-adjusted body weight loss, while Phentermine/Topiramate (not available in Europe), Liraglutide and Naltrexone/Bupropion induce a mean body weight loss of -9.2%, -8% and -5.6%, respectively [2]. Setmelanotide is used in some cases of syndromic or hypothalamic obesity [3].

Over the past decade, three receptors have stood out as key therapeutic targets for obesity treatment: the glucagon-like peptide-1 (GLP-1) receptor, the glucose-dependent insulinotropic polypeptide (GIP) receptor, and the glucagon receptor.

Research priorities

Exploring (and exploiting) the universe of GLP-1, GIP and glucagon

Novel anti-obesity medications that exploit these gut hormones pathways are achieving weight loss outcomes in clinical trials that approach the effectiveness of bariatric surgery. These drugs act both centrally and peripherally to reduce food intake and cravings while enhancing the sense of satiety.

Semaglutide, a GLP-1 receptor agonist, has reached -14.9% weight loss in clinical trials [4]; Tirzepatide, a dual GIP and GLP-1 receptor agonist, reaches an impressive weight loss of – 20.9% [5], making them the currently most potent weight loss drugs on the market. Retatrutide, a triple GLP-1,

GIP and glucagon agonist, currently undergoing phase-3 clinical trials, has shown to reach, at maximum dose, a mean weight loss of −24.2% at 48 weeks [6]. These medications are all in injectable form.

GIP, as GLP-1, stimulates glucose-dependent insulin secretion and decreases appetite. In type 2 diabetes mellitus (T2DM), GIP secretion is preserved, but its insulinotropic action is reduced [7]. GIP carries a protective effect against GLP-1 induced nausea and has a role in lipid deposition and lipogenesis [8]. It is particularly fascinating that GIP antagonism, similarly to GIP agonism, is also linked to weight loss for mechanisms that are not completely clarified; an investigational drug that combines GIPR antagonist and a GLP-1 RA is undergoing phase-2 trials [9].

Glucagon agonism reduces food intake, triggers lipolysis and seems to increase energy expenditure [10]. Glucagon can also activate the GLP-1 receptor on beta cells, stimulating insulin secretion in a paracrine way [10], while the combination with GLP-1 and/or GIP receptor agonists (RA) protects against glucagon-induced hyperglycemia. Survodutide and Mazdutide are GLP-1 RA combined with a glucagon receptor agonist that are currently undergoing phase 3 trials.

Concerning the oral route, oral Semaglutide, which has been available for some years for T2DM treatment at a different dosage, has completed phase-3 trials for obesity indication, showing a mean weight loss of −17.4% [11]. Orforglipron, an oral, partial GLP1-1 RA, that is biased towards G-protein activation over to β-arrestin recruitment at the GLP-1 receptor, is undergoing phase-3 trials for obesity treatment [12].

Other gut hormones receptors as potential therapeutic targets

Amylin acts on amylin receptors in the brainstem to reduce food intake and improves glucose levels by delaying gastric emptying and inhibiting glucagon secretion [13]. Cagrilintide, an amylin analogue, in combination with Semaglutide (CagriSema) is undergoing phase 3 trials. The addition of amylin agonism to GLP-1 R agonism seems to produce a favorable effect on weight loss in diabetes [14], which is notoriously a condition where obesity is more difficult to tackle.

Besides GLP-1, studies have shown that GLP-2 is also involved in beta cell survival and pancreatic islet cell adaptations to stress; GLP-2 receptor agonists, which are currently used to treat intestinal insufficiency, have been combined with GLP-1 RA in double agonists (dapiglutide) that are currently undergoing phase 2 trials for obesity [15, 16].

Thinking outside the gut

Besides gut hormones analogues and antagonists, other medications that exploit different mechanisms could be on the horizon, like Bimagrumab, an IV-administered monoclonal antibody directed against activin type 2 receptor (ActRII), that stimulates skeletal muscle growth and that could be of use in sarcopenic obesity [17]. Another possible target on the horizon is growth/differentiation factor-15 (GDF-15) receptor, as observations highlighted that elevated cancer-secreted GDF-15 increases satiety and induces weight loss by acting centrally [18].

Phase 1 trials are underway for drugs targeting neural populations in the nucleus of the solitary tract that express not only GLP-1 receptors but also the calcitonin receptor (Calcr). Preclinical studies have demonstrated that activating various neuronal populations within the dorsal-vagal complex reduces feeding behavior in rodents [19].

Other pre-clinical therapeutic targets

Fibroblast growth factor 21 (FGF21) is a cytokine that is induced by a wide range of stress conditions (like prolonged fasting) and aims to restore metabolic homeostasis [20]. In obesity, insulin resistance

and fatty liver disease, FGF21 is usually elevated as a consequence of an impairment in its signalling. FGF21 is also involved in dietary preference and appetite, and its levels have been described to rise in response to hypercaloric carbohydrate- or fat-rich diet [21]. FGF21 has, however, poor pharmacokinetic properties. Experiments on ob/ob mice that used viral vectors to increase the endogenous production of FGF21 resulted in significant weight loss, but also led to adipose tissue hypertrophy and inflammation, and hepatic steatosis [22]. Despite these issues, the magnitude of weight loss observed in preclinical models suggests that FGF21 could become a potential therapeutic target for obesity in the coming years.

The cannabinoid type 1 receptor (CB1R) is a clinically validated therapeutic target in obesity, that was exploited in the early 2000s with rimonabant [23]. Recent advancements have led to the development of new-generation CB1R inverse agonists with significantly reduced brain penetration compared to rimonabant, targeting peripheral CB1R receptors [23, 24]. These new agents induce substantial weight loss in mouse models, particularly when combined with incretin analogues, as they exploit a different yet very effective pathway in the treatment of obesity [23].

Brown adipose tissue (BAT) is another interesting and biologically plausible target for obesity. It has the unique feature to generate heat from its own triglycerides content thanks to the presence and the activation of uncoupling protein 1 (UCP1) [25]. BAT is activated mainly via the sympathetic nervous system and it has a physiological glucose-lowering action that is often reduced in insulin resistance (without a concomitant reduction of BAT thermogenic activity) [25]. In the years, many natural and chemical UCP1 activators have been identified [26] and some drugs have been found to induce a metabolic activation of BAT, mainly sympathomimetic drugs such as phentermine, sibutramine, fenfluramine etc., and PPAR-γ agonists like pioglitazone (but also transient receptor potential vanilloide 1 (TRVP1) and G protein–coupled bile acid receptor Gpbar1 (TGR5) agonists) [25]. However, no drug thus far, not even the most recent β-3 adrenergic agonist mirabegron, could demonstrate to selectively activate BAT in humans without inducing cardiac chronotropic effects [25].

Anticipated impact of future research

The future will be in oral medications

Besides exploring new therapeutic targets, research is also focusing on developing medications with simpler, less burdensome (and less costly) routes of administration.

Oral delivery of pharmacotherapy is especially desirable, but it has faced substantial barriers so far due to the structure of the gastrointestinal tract, that physiologically hinders the free passage of peptides through the intestinal epithelium. Oral semaglutide, mentioned above, contains an absorption enhancer that facilitates uptake through gastric mucosa [27]. New-generation oral drugs like orforglipron are called “small-molecule” agonists, that is they are ligands of the GLP-1 receptor that work via an allosteric mode to partially agonise the GLP-1 receptor [12, 28]. They are biased towards toward Gαs protein recruitment, favouring cAMP production, over β-arrestin (differently from “older” GLP-1 RA) [29]. Altered receptor engagement leads to retention of the GLP-1 receptor on the cell surface and continued signaling over a prolonged time [30]. This bias, which is thought to be exploited also by tirzepatide [31], ultimately leads to a more robust response and increases the potency of the drug on HbA1c and weight loss [30].

Differently from injectable GLP1-RA, oral “small-molecule” non-peptide GLP1-RA are also easy to manufacture [30].

Given the anticipated high demand for GLP-1 RA therapy in the future, the potency, simple route of administration, and ease of manufacture of these drugs make them convincing candidates for treatment of obesity and T2DM.

Towards tailored pharmacological treatment based on obesity-related complications

Obesity is strongly associated with T2DM, and when these two conditions co-exist, patients generally achieve less weight loss compared to those without diabetes. For example, in clinical trials, weight loss at 68 weeks with Semaglutide 2.4 mg was -9.6% in T2DM patients vs -14.9 in non-diabetic patients, despite similar lifestyle intervention [4, 32]. This highlights the need for even more potent medications to effectively address obesity in diabetic obese patients.

Obesity also significantly increases the risk of cardiovascular disease, metabolic dysfunction associated steatotic liver disease (MASLD), and mechanical complications such as osteoarthritis and obstructive sleep apnoea (OSA). Some newer obesity medications exhibit direct and weight-independent effects on ectopic fat deposition, which contributes to cardiac and metabolic dysfunction. For example, combinations of GLP-1 plus glucagon receptor agonists have been shown to reduce liver fat content in people with MASLD more effectively than GLP-1 RA alone, despite similar weight loss, due to a direct effect of glucagon on hepatic lipid oxidation [33]. Yet, GLP-1 RAs alone reduce epicardial fat and Semaglutide has shown to improve physical limitations and symptoms in people with obesity and heart failure with preserved ejection fraction (HFpEF) [34]. The dual GLP-1/GIP agonist Tirzepatide has convincing evidence for treating OSA in patients with obesity [35].

Furthermore, patient preferences, such as an aversion to injections, may influence treatment choices. Future research will further elucidate the potential, as well as the limitations, of each compound in addressing obesity-related complications, paving the way for tailored pharmacotherapy that meets individual patient needs.

Key points:

- Novel antiobesity medications like Semaglutide and Tirzepatide have opened a new era in the treatment of obesity and T2DM, reaching weight loss of up to 15-21%.
- A plethora of new drugs, that exploit the incretin system receptors (glucagon, amylin, GLP-2) and/or that specifically target receptors outside the gut (ActRII in the muscle, CalcR and GDF-15 R in the brain), will become available in the coming years, while research is making progress on other promising targets (FGF21, CB1R, BAT).
- Future pharmacological therapy of obesity will be less costly and burdensome, possibly in the oral form, and tailored based on obesity-related complications (and patient preferences).

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Behavioural modification for obesity and type 2 diabetes

[redacted]

The current state of the art

Behavioural modification is the central component of lifestyle interventions (LSI) which are considered the cornerstone approach for the management of obesity and type 2 diabetes (T2D) (1, 2). According to the findings from pioneer LSI trials – such as the Look AHEAD study (3), the DDP Program (DPP) (4), and others (5, 6), in which their study design placed behavioural modification (i.e., strategies) as a key element, combined with diet and physical activity – a significant body weight loss was associated with benefits in medical and psychosocial outcomes, which is foremost in the prevention and treatment of T2D, at least over the short and intermediate terms (7). However, despite this fact, in real-world clinical settings the implications of LSI based on behavioural modification are not that significant, and it seems that they are not fully or properly delivered according to their real potential in populations with obesity and/or T2D (8, 9).

Research priorities in the following areas

The discrepancies between the effectiveness of LSI based on behavioural modification in research settings and non/partial efficacy in real-world clinical settings are questionable and still not fully understood. These may be attributable to certain shortcomings in the research which would need investigating in future research (8, 9):

2.1. Standardization of LSI based on behavioural modification

According to the literature, the use of the terminology of LSI based on behavioural modification in both clinical and research settings is broad, ranging from the Naïf educational approaches based on rigid prescriptions (i.e., diet and exercise) to more articulated programmes which include behavioural strategies as key components (10-12), and this has made their success arguable in the management of obesity and T2D (8). Therefore, firstly, cornerstone research action is needed, with the conduct of rigorous "systematic reviews and meta-analysis" from which a consensus about a standardized LSI based on modification behaviour can be established (13). It is expected that the proposed standardized programme(s) should include more effective behavioural strategies than have thus far been identified in previous well-conducted research (1, 14). However, at the same time, the proposed standardized programme(s) should be more simplified than previous programmes so as to be easily deliverable by any healthcare professional, as well as manual-based to be fluid in skills transferability, and be patient-centred with a self-administered option so as to meet patients' needs (15). Therefore, there needs to be a clear description based on a protocol (i.e., personalized but standard in content, duration and procedures), and for the programme to be properly adaptable for any public health setting (i.e., foremost primary care) and clinical setting (specialized outpatient and inpatient, including mental health and bariatric surgery settings), as well as usable across different populations (children, adolescents, middle-age adults, and the elderly) and ethnicities (e.g., Asian, Middle Eastern, European and America) (16, 17).

2.2. Studies on the effectiveness and identification of new successful behavioural strategies

Studies of the effectiveness on LSI based on behavioural modification should be conducted to improve such programme(s) and enrich them with new behavioural strategies (14). Moreover, studies that identify new strategies that lead to an increase in patient motivation and adherence to these programme(s) and reduce the rates of attrition and dropout are crucial, especially in the long term, since the beneficial effect of LSI based on behaviour modification programmes are not maintained with time (11). For this reason, the effectiveness of such programmes should also be tested at different clinical settings as well as at different intensities (i.e., duration of programme, number of sessions, health profession involved) and ways of delivery (e.g., individual or in a group, in-person or through telemedicine or apps) and, last but not least, in combination with other

therapeutic approaches for obesity and T2D, such as anti-obesity/anti-diabetic medications and/or bariatric/metabolic surgery.

2.3. Studies on training and dissemination

The research on how to improve training in and dissemination of LSI programmes based on behavioural modification among health professionals on a wide scale and their implementation at different levels of clinical setting are of extreme importance (18). In this direction, research should identify the most effective training modalities, and at the same time consider the ease of dissemination and deliverability (i.e., be cost-effective). To complement this research area, the professional skills and competence of the healthcare professionals that are delivering these programmes, as well their attitude with regard to how regularly they propose them to their patients should always be assessed and considered as a subject of improvement (19). Nowadays, technological advancements cannot be ignored, therefore new studies should consider testing the effectiveness of web-based training and dissemination-by-distance, in order to involve as many healthcare professionals as possible, regardless any logistical obstacles (geographical location, finances, etc.) (20).

Anticipated future impact

Briefly, the anticipated future impact of conducting this research will be to crystallize the concept of behavioural modification as a standardized approach(s) composed of specific procedures as with any other medical intervention. This will facilitate the task of assessing their effectiveness and render them improvable in terms of the identification of more new and effective behavioural strategies and better outcomes. Moreover, the investment in new research that aims to improve training in LSI based on behavioural modification and its dissemination, especially taking into account strategies for technological advancement, will make these programmes through web-training and dissemination-by-distance more accessible to a wide range of healthcare professionals, and also more easily accessible for patients through the use of telemedicine and apps.

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Personalised targeted therapy for monogenic obesity/ diabetes: including leptin-melanocortin pathway (metreleptin, setmelanotide) and gene therapy for diabetes/obesity

[redacted]

1. Epidemiology, societal impact and current state of the art

Recent focus has been directed towards the genetics underlying obesity, providing insights into the inherent physiological and molecular mechanisms that regulate body weight. The melanocortin-4 receptor (MC4R) pathway plays a crucial role in the regulation of appetite and energy balance. Pathogenic mutations in MC4R are identified in up to 5% of cases of severe childhood obesity and up to 0.3% of the general population (PMID:34045736, PMID:12646665). Mutations in LEPR are found in

3-4% of patients with severe obesity (PMID:17229951, PMID:25751111). Furthermore, the prevalence of monogenic obesity could reach up to 30% in populations with a high consanguinity (PMID:26179253). The discovery of these obesity forms has been pivotal in identifying key mechanisms of appetite control has facilitated the development of new pharmaceutical treatments. However, extensive preclinical research, particularly additional studies in paediatric populations, is essential to translate these innovative treatment approaches into clinical practice.

For monogenic diabetes, there has been a dramatic increase in discovery of underlying genetic causes of neonatal diabetes with 82% of cases now having a genetic diagnosis (PMID: 31479665). Later onset monogenic diabetes, largely Maturity Onset Diabetes of the Young (MODY) there remains a significant proportion of cases where genetic aetiology cannot be established (called MODY X), possibly due to misclassification. Identifying a genetic aetiology of diabetes can have a life-changing impact on treatment. Almost all patients with neonatal diabetes due to an activating mutation in one of the genes encoding the potassium channel mutation can be successfully transitioned off insulin on to oral sulphonylurea treatment with near normalisation of blood sugar (PMID 16885550), an effect that seems to persist long term (PMID: 29880308). For patients with MODY due to HNF1A and HNF4A, patients are exquisitely sensitive to low dose sulphonylureas and again if insulin treated can often transition off insulin (PMID: 14575972). There remain a number of key challenges – in both implementation, discovery and treatment.

2. Research priorities – Monogenic obesity

The primary future research areas in treatment of monogenic obesity are focused on the advancement of personalized medicine.

2.1. Lifestyle modification therapies:

The limited efficacy of lifestyle interventions in individuals with monogenic obesity is due to their inability to specifically address the underlying physiological abnormalities triggering obesity.

a. Further research is necessary to enhance understanding of the impact of lifestyle interventions in monogenic obesity to tailor treatment more effectively.

b. There is an urgent need for more personalized prevention and treatment strategies. Nutritional and exercise genomics or metabolomic evaluations might be useful and beneficial.

2.2. Pharmacological treatment:

In the recent years, genetic studies have enabled personalized treatment options for certain types of monogenic obesity.

a. GLP-1 analogues: Current evidence suggested a maintained efficacy of GLP-1 agonists in genetic obesity characterized by impaired MC4R pathway. Further studies are needed for the long-term effects of GLP-1 analogues in MC4R mutations. Additionally, exploring the effects of GLP-1 analogues in patients with monogenic obesity caused by other mutations would be of significant interest.

b. Leptin: Leptin has been implicated in promoting cancer progression through activation of pro-proliferative or anti-apoptotic pathways (PMID: 33857282). Future studies are essential to establish a causal relationship between leptin treatment and the pathogenesis of obesity-related cancers as a long-term effect.

c. MC4R agonists (Setmelanotide): The medium and long-term side effects of setmelanotide should be monitored, especially evaluating the consequences of chronic stimulation of

melanocytes. Although there some explanations, the variety in weight loss between patients with different mutations in MC4R pathway emphasizes a further need to understand the mechanisms. Another research area is the potential benefit of MC4R agonists for patients with common polygenic obesity.

d. Unimolecular polypharmacology: Dual or triple incretin based drugs are currently being approved as potential therapies for obesity and there is an emerging necessity to investigate their effectiveness in specific types of monogenic obesity.

e. Oxytocin: Further studies are required to elucidate the effect of oxytocin therapy on appetite and to explore the attributes of novel oxytocin mimetic peptides in monogenic obesity.

2.3. Gene Therapy:

Patients with monogenic obesity might benefit from novel treatment technologies.

a. CRISPR and Gene editing: Gene-editing technologies (CRISPR) has been tried in leptin-deficient, obese ob/ob mice using an adenoviral CRISPR system and the production of leptin and its physiological functions were restored (PMID: 33931338). Future research is needed to focus on delivery methods, off-target effects, long-term efficacy and safety of these technologies.

b. Antisense oligonucleotides (ASOs): ASOs are another promising treatment modality. Despite limitation in crossing the blood-brain barier, future studies are needed to explore their effectiveness in monogenic obesity.

2.4. Bariatric Surgery:

It is crucial to consider that bariatric surgery may be the only beneficial management option in the presence of a life-threatening comorbidities in patients with monogenic obesity. Further studies are required to evauate the long-term safety and efficacy of bariatric surgery in monogenic obesity. Also, additional studies are necessary to elucidate the correlation between functional characteristics of MC4R pathway variants and long-term weight trajectories after the surgery.

3. Research Priorities – Monogenic Diabetes

3.1. Global implementation of appropriate testing strategies and subsequent appropriate treatment to ensure benefits of well established pharmacogenetic effects. In most low or middle income countries there is either no testing for monogenic diabetes or there is very limited access for most members of the population. The most obvious area where testing is inadequate sub-Saharan Africa. Different strategies are needed in white European populations and other ethnicities especially when a high prevalence of slim young onset Type 2 diabetes or a high prevalence of consanguinity (PMID 34686905 PMID 27435864)

3.2. Novel causes of MODY need to be identified There are a considerable number individuals who have all the characteristics of MODY who do not have the presently defined genetic aetiologies. These may reflect genes with reduced penetrance like RFX6 (PMID: 29026101) or high polygenic burden or a combination of the two.

3.3. Novel causes of neonatal diabetes need to be identified There are individuals with early-onset neonatal diabetes where all the 38 known causes have been excluded. These aetiologies need to be identified as they give crucial insights into the development, function and destruction of the human beta-cell.

3.4. Improved understanding and therapy for the Neurological deficits due to the potassium channel mutations. Work is needed to understand the range of deficit from mild to severe seen in

patients with mutations in the KATP channel resulting in neonatal diabetes and MODY. For those with severe intellectual impairment there is some response to sulphonylurea which needs further investigation and other therapies that have better brain penetrance should be investigated. (PMID: 24622368, PMID: 33184150,PMID: 30377186,PMID: 28477417)

3.5. Understanding of modifiers genetic and non genetic that alter penetrance of pathological mutations in monogenic diabetes There is evidence in almost all subtypes of monogenic factors of variable penetrance of the same monogenic aetiological variant. This needs to be investigated to see if there are definable modifiers such as polygenic risk scores or epigenetic modification during maternal diabetic pregnancy that alters age of diagnosis by >10 years. (PMID: 36257325, PMID: 12453975)

4. Anticipated future impact

Furher studies focusing on gene therapy, pharmacological advancements, personalized treatment strategies, and long-term effects can facilitate the development of more effective and individualized treatments. These efforts will not only benefit individuals with monogenic obesity and diabetes but also provide insights applicable common obesity and diabetes.

Novel drug targets: dual receptor agonists for obesity and/or type 2 diabetes

[redacted]

Epidemiology, societal impact and current state of the art

GLP-1 receptor (GLP-1R) agonists reduce weight primarily through decreased food intake and delayed gastric emptying. However, their efficacy is often limited by adverse effects such as nausea, which can lead to discontinuation of the treatment (Sikirica et al., 2017). Gastric inhibitory polypeptide (GIP) plays a crucial role in energy metabolism. It stimulates insulin secretion, therefore lowering blood glucose levels. Additionally, GIP acts on the central nervous system to reduce food intake and body weight. Novel dual-agonists targeting both GLP-1R and GIP receptors (tirzepatide) or glucagon receptors (GCGR) (cotadutide) represent a promising therapeutic strategy. These combination therapies can achieve over 10% sustained weight loss in patients, with at least 8 out of 10 patients achieving clinically significant weight loss of more than 5% (Garvey et al., 2023; Jastreboff et al., 2022). They do not only enhance insulin secretion and improve glycemic control but also mitigate the adverse effects commonly associated with GLP-1R agonists alone. For instance, GIP receptor (GIPR) agonist treatment has been shown to protect against nausea and anorexic behaviors in mice (Borner et al., 2020; Samms et al., 2020).

Research priorities

Research on tissue-specific underlying mechansims

Research into the tissue-specific mechanisms of dual-agonists will enhance our understanding of how these medications exert their effects at a cellular level as these mechanism still remain to be elucidated.

Both GIP receptor (GIPR) agonists and antagonists have been shown to prevent obesity, as evidenced by studies demonstrating that GIPR antagonism can reduce weight gain in mice (Miyawaki et al., 2002). These paradoxically contradictory mechanisms of action of GIP have not yet been fully explained. Additionally, tirzepatide has been shown to increase energy expenditure and lower respiratory exchange ratios, indicating a shift towards increased whole-body lipid oxidation. However, the specific underlying mechanism remains unclear (Coskun et al., 2018).

Individualized Therapy

Personalizing dual-agonist therapy based on individual patient profiles and comorbidities is of great importance. To this end, it is essential to determine which patient groups can benefit the most from specific agonists. The SURMOUNT-1 and -2 studies suggest that individuals with obesity, but without type 2 diabetes (T2DM), experience greater weight loss with GLP-1R/GIPR agonist therapy compared to those with T2DM of similar BMI (Garvey et al., 2023; Jastreboff et al., 2022). Additionally, tirzepatide as well as cotadutide have shown promise in reducing non-alcoholic steatohepatitis (NASH) biomarkers in T2DM patients, indicating potential benefits beyond glycemic control and weight loss (Hartman et al., 2020). Comparative studies and mechanistic investigations are necessary to understand these effects and tailor treatments accordingly.

Long-Term Trials and Dose variations

Conducting long-term clinical trials to assess the safety and efficacy of dual-agonists at higher doses is crucial. Comparing GLP-1R agonists, longer-acting GIP and GLP-1R agonists, and dual-agonists will provide insights into optimal dosing and long-term outcomes. These studies should also evaluate the benefits of combining pharmacotherapy with lifestyle interventions like diet and exercise. Additionally, assessing dual-agonists in children and adolescents is essential due to the rising rates of obesity and T2DM in younger populations.

Anticipated future impact

The recent completion of clinical trials such as SURMOUNT-3 and -4, with SURMOUNT-5 expected to conclude in January 2025, will be crucial for validating the benefits observed in earlier studies and for informing regulatory approvals and clinical guidelines. Positive outcomes from these trials could lead to widespread adoption of tirzepatide and similar dual-agonists in clinical practice, offering new hope for patients struggling with obesity and T2DM. One challenge is the risk of metabolic health decline upon cessation of pharmacological treatment. Research to address this problem is crucial in order to provide strategies like gradual dose reduction of combination with behavioral interventions to mitigate the relapse.

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Novel drug targets: incretin mimetics for obesity and/or type 2 diabetes

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Diabetes mellitus represents the global medical, economic, and social problem due to the high and growing prevalence of disease, the risk of micro-, macrovascular, and neurological complications which lead to the significantly increased morbidity, mortality and economic costs associated with diabetes. International Diabetes Federation (IDF) Diabetes Atlas reports that 10.5% of the adult population (20-79 years) has diabetes, with almost half unaware that they are living with the condition (2021). The total number of people with diabetes mellitus worldwide in 2021 was 537 million, increasing to 643 million in 2030 and it is estimated that by 2045 1 in 8 adults, approximately 783 million, will be living with diabetes, an increase of 46%.

Over 90% of people with diabetes have type 2 diabetes, which is driven by socio-economic, demographic, environmental, and genetic factors which are urbanization, an ageing population, decreasing levels of physical activity and increasing prevalence of overweight and obesity.

Approximately 80% of patients with type 2 diabetes are obese or overweight. Therefore, according to the majority of the current guidelines the control of body weight represents one of the most important directions for the successful prevention and treatment of type 2 diabetes mellitus (ADA/EASD Consensus Report, 2022; ADA Standards of Care, 2024 and others).

The development and active implementation of new effective tools to decrease and maintain body weight addressing the targets related to the pathophysiology of type 2 diabetes are the one of the main priorities of the research in this area.

The introduction in the clinical practice of the new antihyperglycemic medications, GLP-1 receptors agonists, led to the significant improvement of diabetes control, which was accompanied by the dramatic decrease of body weight in the majority of cases and, which seems to be the most important, to the significant reduction of cardiovascular morbidity and mortality not just in patients with type 2 diabetes mellitus but in subjects with obesity without diabetes. Such positive actions of this class of medications, GLP-1 agonists, are attributed to their numerous effects such as increased insulin biosynthesis and improvement of beta-cell function; decreased the hepatic glucose production, lipogenesis in the liver, steatosis and increased hepatic insulin sensitivity; decreased lipotoxicity; increased satiety and consequently decreased food intake and body weight; decreased glucagon secretion; decreased gastric emptying; increased natriuresis, diuresis, decreased

inflammation and oxidative stress in kidneys; increased insulin sensitivity in muscles (DeFronzo et al., 2017).

In the randomized clinical trials enrolling patients with type 2 diabetes mellitus GLP-1 agonists have shown the ability to significantly decrease the risk of myocardial infarction, stroke and cardiovascular mortality compared to placebo on the top of standard antihyperglycemic treatment. In LEADER trial liraglutide reduced such a risk by 13%, in SUSTAIN-6 semaglutide reduced the risk by 26%, and in REWIND dulaglutide decreased the risk by 12%. The positive effects of GLP-1 agonists are not restricted to the reduction of cardiovascular macrovascular complications. Recently, it was announced that in FLOW study semaglutide reduced the risk of kidney-disease progression as well as cardiovascular and kidney death by 24% in patients with type 2 diabetes compared to placebo.

GLP-1 agonists were shown to be effective in reducing the cardiovascular morbidity and mortality in the recently presented SELECT trial which enrolled subjects with obesity without diabetes. Semaglutide reduced the risk of myocardial infarction, stroke, and cardiovascular mortality by 20% (Linoff et al., 2024).

There are important and exciting data regarding the new medications in this area which have dual or even triple mechanisms of action. For instance, tirzepatide, which acts on GLP-1 and glucose-dependent insulinotropic polypetide (GIP) receptors has shown even the higher potency in reducing the body weight. Other medications acting on other incretins are at the advanced stages of development.

GlP-1 agonists are promising as the new tool for the treatment of other diseases such as metabolic-dysfunction associated liver disease, neurodegenerative diseases (cognitive impairments, Alzheimer disease) due to the various pleiotropic mechanisms of action of these medications.

Microbiome shotgun sequencing in guiding nutritional strategy

[redacted]

Epidemiology, societal impact and current state of the art

The human gut microbiome (microbiota) is a complex living bacterial community inside the gastrointestinal tract, consisting of trillions of microorganisms together with their genes which are symbiotic in healthy body (1,2). Each person has a unique microbiota includes bacteria, viruses, fungi, archaea and protozoa which can be partially changed under the influence of various factors throughout the life. Different taxonomy and higher gut bacterial diversity was observed in lean than in obese people (3). Balanced microbiota acts protectively on the intestinal mucosa, while dysbiosis can cause increased bowel permeability, resulting in inflammation and metabolic imbalance. It is possible to modulate microbiota using different lifestyle and dietary factors. Nutrition, especially dietary fibers significantly affects the amount and type of gut bacteria (1-3). Current experience referring to the connection between genes of microbiota and nutrition is limited due to complicated techniques that were used for microbiota gene detection (2).

Research priority

The first aim of the research is to explore gut microbial profile in people with metabolic diseases (eg. obesity, metabolic syndrome, diabetes type 2). In order to understand the heterogeneity of genes within a species or within a population, metagenomic and metataxonomic strategies should be used. Previous studies of microbiota composition demonstrated that shotgun sequencing is more powerful in identifying bacterial species than the usual 16S rRNA genome sequencing method. Deep metagenomic sequencing (DS), with more than 10 million reads per sample, is a reliable method for revealing taxonomic composition and gene profiles but is expensive for large studies. An alternative

to DS and 16S metagenomic sequencing is shallow shotgun metagenomic sequencing (SS). SS has between 2 and 5 million reads per sample, is non-inferior to DS in terms of functional gene sequence and taxonomy, and is more cost-effective for large-scale screening studies (4). The way to identify the taxonomic composition of the microbiota in metabolic diseases is by using the SS method to determine the relative abundance of individual taxa. One of the challenges of metagenomic research is the assessment of the genetic contribution of each member of the taxonomic community (5).

The second goal is to establish a change in the composition and abundance of the microbiota after different diets (such as Mediterranean diet, ketogenic diet, diets with different type and amounts of dietary fiber, etc) or use of probiotics.

The third objective is to monitor the impact of changes in the microbiota after the intervention, on metabolic and inflammatory parameters such as blood glucose, insulin, lipids, hsCRP, IL6, and TNFα.

Anticipated future impact

Analysis of the microbiota using shotgun sequencing method will enable an individual approach in the selection of medical nutritional therapy or probiotics in order to establish a strategy to combat obesity, insulin resistance and associated metabolic disorders.

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Next generation sequencing in guiding nutritional strategy in diabetes/obesity

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Epidemiology, societal impact and current state of the art

A serious public health concern globally is the rise of the numbers of people with chronic metabolic diseases such as obesity and diabetes. Food and nutrition are essential parts of the management of metabolic diseases.[1] Still there is no consensus on the ideal nutritional strategy and percentages of calories, carbohydrates, proteins, and fats for people with diabetes and obesity.[2] Results of recent human clinical studies have shown that blood glucose levels change differently in different people in response to the same standardized meals.[3] Thus a one-size-fits-all approach does not work in a population with diverse genetic background and dietary practices.

The goal of precision nutrition is to provide more precise and dynamic nutritional recommendations than currently possible through population-wide guidance (NIH, 2020). Next-generation sequencing (NGS) is a powerful tool used in genomics research, providing comprehensive insights into genome structure, genetic variations, gene expression profiles, and epigenetic modifications. NGS paved the way for a new era of personalised medicine and personal genomics. Its affordability allowed the initiation of many national and international population-scale sequencing strategies and programmes including the genomes of thousands or even millions of individuals combined with detailed medical and lifestyle information.

Research priorities

Obesity and diabetes are polygenic and multifactorial conditions that result from interaction between genes and environmental factors, with a bidirectional relationship between genome and nutrition. Nutrigenetics is the science that studies and characterizes gene variants associated with differential response to specific nutrients, relating this variation to various diseases, such as diabetes and obesity. [4] Nutrigenomics explores the interaction between genes and nutrients and their effects on human health as nutrients up- or downregulate the gene expression, and consequently, at the molecular level, the metabolic responses.[5]

Genome-wide association studies (GWAS) including a constantly increasing number of individuals and biostatistical meta-analyses of the generated data is needed in order to decipher the role and effectiveness of different dietary regimens in individuals with obesity and diabetes. Different polygenic risk scoring (PRS) approaches need to be developed and optimised in order to become more precise in predicting the metabolic profile and the body's response to different nutrients, as well as in tailoring a personalised diet. [6-8]

There is insufficient evidence demonstrating the superiority of precision nutrition over traditional dietary recommendations which needs to be studied.

Therefore personalized nutrition research is needed and should focus on:

- Identification of genetic variants (SNPs) that influence intake and metabolism of specific nutrients and predict individuals' variability in response to dietary interventions.
- Identification of genetic variants (SNPs) related to postprandial glucose levels, insulin and regulation of energy homeostasis
- how different diets (high-fat, low-fat, low-carbohydrate, ketogenic, Mediterranean) interact with genetic variants and influence disease severity in patients with diabetes/obesity

The substantial progress of long-read sequencing technologies ("third generation") constantly expands the knowledge of the structural variation in the genome and could also identify new structural variants associated with nutritional response and dietary effectiveness.

Anticipated future impact

Recent advancements in NGS hold great promise for unlocking new insights into genomics and improving the understanding of diseases and personalized healthcare.[9] Identification of a wider spectrum of genetic factors that play a role in the diet-metabolic disease relationship could lead to a better understanding of what the optimal diet for an individual is. Personal genetic profiling of the metabolism and physiology will in turn lead to personalised nutrition recommendations based on the complex network of genetic variants carried. This could dramatically improve the outcomes of specific dietary interventions and could represent a new nutritional approach to improve health, reducing obesity and diabetes.

The integration of precision nutrition into routine clinical practice requires further validation through randomized controlled trials and the accumulation of a larger body of evidence to strengthen its foundation.[10]

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Subtopic 3: Type 1 Diabetes Management and Treatment

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1. Type 1 Diabetes Management and Treatment: Epidemiology, societal impact, and research state of the art

Type 1 diabetes (T1D) is the most common metabolic disorder in children and has a lifelong impact on those affected and their families or caregivers. Over the last decades, a steady rise in the incidence of T1D is observed (1). Importantly, this disease still carries a high burden of morbidity and increased risk of (mostly cardiovascular) mortality, with children developing T1D before the age of 10 years losing on average 14-17 years of life expectancy (2).

T1D manifests as a complex interplay between polygenic predisposition and environmental influences. Genes and environmental factors combine to break down the immune tolerance towards self-antigens, leading to the autoimmune-mediated destruction of the insulin-producing beta cells within the pancreas. Although T1D predominantly emerges during childhood and adolescence, half of all T1D diagnoses occur beyond the age of 18 years.

T1D is the archetype model of autoimmunity, which is the underlying mechanism of disease, affecting 9 million people worldwide (3). In Europe, approximately 300,000 children and adolescents are affected by T1D with an annual incidence rate of 15 new diagnoses per 100,000 European citizens. At the point of T1D diagnosis, a considerable portion of individuals, particularly children, experience substantial morbidity, often necessitating hospitalization and intensive care admission due to diabetic ketoacidosis (DKA). This acute metabolic complication affects up to 50 percent of children during their initial clinical presentation of T1D (4). DKA is not only a life-threatening condition at the time of diagnosis but has a lifelong impact on metabolic control and cognitive function. Despite many educational initiatives, DKA continues to be prevalent during the initial manifestation and diagnosis of T1D in 2024.

Since the discovery of insulin over a century ago, insulin therapy has transformed T1D from an acutely lethal disorder into a chronic disease. However, treatment of T1D based on insulin replacement therapy often fails to achieve physiological glycaemic control despite major advances in insulin analogues and novel technologies for glucose monitoring and insulin delivery. This is particularly true in children, where the physical and/or psychological burden on those affected and their families is greatest. As a result of chronic dysglycaemia, people with T1D are at high risk of acute and chronic complications. Mortality and morbidity in T1D are closely correlated with the quality of metabolic control, residual beta-cell function, and the duration of exposure to the disease.

On top of the burden T1D places on patients and their families, diabetes is an expensive disease, with an important economic impact on health care systems, with an estimated annual cost of T1D in Europe of more than 30,000 million euros. Recent work by JDRF highlighted the potential impact of screening and diagnosis of T1D in preclinical stages on the societal cost of T1D (5). The cost of treating one patient over a 25-year period is in the range of 100,000 to 200,000 euros. Next to these direct costs, indirect costs and emotional burden need to be considered. While most of those suffering with the disease are living in high-income countries, inequities in access to care still pose a challenge and most of the current research still lacks the diversity necessary to optimize personalized care. Both health inequalities and T1D are increasing. For example, research has demonstrated a higher prevalence of T1D, more barriers to diabetes care and less frequent use of advanced technology such as insulin pumps and glucose sensors among ethnic communities (6). Addressing health inequalities is crucial to ensuring equitable health outcomes for all individuals living with T1D.

Social determinants of health play a significant role in shaping health outcomes and they contribute to health inequalities within populations with T1D. Even in our European environment, social determinants of health such as income, education, housing and transportation, stigma and discrimination, health literacy, and social support can contribute to the overall burden, significantly affecting the health and wellbeing of individuals and communities (7). More research is needed to understand the role of social issues in the prevention and management of T1D, including qualitative studies to understand how we can address social barriers to access T1D care and how to provide social support to patients across communities.

2. Type 1 Diabetes Management and Treatment: Future Research Priorities

The key future research priorities englobe the 4Cs in Diabetes Type 1 Management and Treatment:

2.1. Concept

a. Disease pathogenesis (e.g. genetics) and heterogeneity

European support has been crucial in advancing our knowledge in the pathogenesis of T1D, discovering novel biomarkers and understanding the heterogeneous character of the disease. Still many questions exist on the genetic markers of the disease, with the need to improve our genetic predictive power, by better understanding the genetic build up leading to T1D. Better biomarkers to help predict those who will develop autoimmunity early or later in life and in particular biomarkers to predict who will progress from pure autoimmune attack of the beta-cell to full blown clinical T1D are needed. Innovative Health Initiative (IHI)-supported projects like INNODIA have collected samples and multiomics data in hundreds of people with newly diagnosed (stage 3) T1D or in preclinical stages (1 and 2). These biosamples collected using highly standardized procedures, and data from multiomics analyses on these samples are available for more in depth research on biomarker discovery. Understanding triggers of disease (and disease progression) and finding better biomarkers of disease progression will help our understanding of the pathogenesis of the disease and identify different disease trajectories that may require different interventions (see below).

b. Screening (novel tools), early detection of T1D

At present we screen for genetic risk of T1D by using genetic risk scores, combining HLA and SNPs of different genes. Further refinement of these tools is needed to improve our genetic risk screening in general population. Parallelly, initiatives of early (preclinical) diagnosis of T1D are ongoing, using detection of antibodies in the blood of participants. Further refinement of the assays of these antibodies is needed, to allow upscaling of the initiatives and also integration into our health care systems. Collaboration between academia and industry is of the utmost importance here. Also monitoring tools for those at risk or with preclinical stages (1 and 2) are to be refined. At present an IHI project (EDENT1FI) is evaluating different paths to screen and exploring the potential of CGM as a monitoring tool. Other methods are needed.

c. Disease modifying therapies in T1D

Our growing insight into the pathogenesis of T1D has brought disease modifying therapies to T1D. However, we need to move on from a one-size-fits-all approach, as heterogeneity in disease trajectories is present and therapies may not work in all. Therefore, research into biomarkers of therapeutic effect (both failure and success) is needed. Also attracting novel disease modifying therapies to Europe is of the utmost importance. A network has been created, INNODIA.org, a spin-off of the IHI projects INNODAI and INNODIA HARVEST, to execute these trials, but more support for attracting these trials to Europe is needed, with emphasis on standardized execution of the trials (using masterprotocols), combination trials and research on biomarkers of effect.

d. Novel endpoints in clinical trials

T1D staging relies on two tests: the measure of islet autoimmunity and the oral glucose tolerance tests, the latter being moderately invasive and poorly reproducible. As a result, current disease staging is unable to describe the actual disease heterogeneity, to accurately estimate the risk for disease progression or to serve as surrogate endpoint in clinical trials involving disease modifying treatments. The need for defining pre-symptomatic disease progression across different age groups challenges the current staging paradigm and requires novel, minimally invasive tools able to accurately track disease progression. Time to clinical disease progression remains the only endpoint accepted by the regulatory agencies in pre-stage 3 T1D, thus limiting clinical trials feasibility due to the need for a relatively large number of people and the inability to design adaptive studies allowing sequential or alternative treatments for those who are deemed non-responder to one or more medications. There is need for

reliable surrogate endpoints able to track disease progression in clinical trials reflecting the actual beta cell function and the time to symptomatic disease.

2.2. Care

a. Wearable technology for early detection (sensors) and disease management

Routine glucose monitoring is fundamental to precisely deliver insulin replacement therapy. Based on a substantial number of clinical trials that have validated efficacy and safety, continuous glucose monitoring (CGM) devices are part of the current standard of care, regardless of age, diabetes type, stage of the disease and insulin delivery modality. CGM use can transform diabetes care by improving glycemia, reducing acute and chronic complications, and improving quality of life (9).

The use of CGM-derived metrics, such as time in range (TIR), time below range (TBR), and time above range (TAR), and unified reporting, presentation, and visualization of CGM data nowadays greatly facilitate the communication between persons with diabetes, their families and health care providers. As CGM devices are becoming more advanced, accurate and broadly accessible, their usability expands beyond the role of insulin dosing titration guidance, including non-insulin treated persons with type 2 diabetes and as an outcome measure for clinical trials. Recently, studies have investigated the use of CGM and CGM-derived thresholds as diagnostic tools for identifying and staging T1D (9-12). Finally, CGM is a core component of glucose-responsive automated insulin delivery (AID) systems (13).

b. Automated insulin delivery (AID)

AID, whether integrated into an insulin pump or as a smartphone/tablet/computer application, consists of a CGM that feeds glucose data to a control algorithm. This algorithm then translates the real-time data it receives and computes the amount of insulin delivered via the insulin pump. AID enables maintaining glucose levels within target ranges more effectively than conventional treatment modalities. This not only reduces the risk of hyperglycaemia and hypoglycaemia but also alleviates the everyday burden of T1D.

Multiple clinical trials using different AID systems and with varying components have been performed in adults (including pregnancy complicated with T1D) and children, demonstrating robust clinical benefits in broader glycaemic outcomes as well as psychosocial benefits (14-19). These observations have been complemented also in the real-world setting, underscoring that access to this technology should be made broadly available and based on the needs of each individual.

c. Software and machine learning approaches

With the exponential increase of data generated by technologies used in diabetes care, machine learning approaches and automated decision support systems might play a crucial role in diabetes care by leveraging extensive quantities of information to enhance disease management, prediction, and treatment personalization (20). These techniques could analyse diverse and broad data sources simultaneously, including electronic health records, CGM data, genetic information, lifestyle factors, and treatment history, to identify patterns, predict outcomes, and optimize interventions.

An automated decision support system can provide insulin therapy adjustment recommendations for diabetes management to healthcare professionals managing individuals with T1D, delivering assistance and elevating the quality of diabetes care where there is a shortage of experienced diabetes care teams (21). Another key application of machine learning in diabetes care is predictive modelling for early detection of microvascular complications such as diabetic retinopathy, neuropathy, and nephropathy. By analysing various risk factors and biomarkers, an algorithm could help identifying individuals at higher risk of developing complications, allowing for timely and person-tailored interventions to prevent or mitigate their progression.

d. Access - equity, diversity and access to care, stigma and quality of life, person-reported outcomes

Living with T1D can be a stressful experience and this can also impact diabetes treatment outcomes (e.g. treatments may work inadequately) as well as self-management strategies (e.g. unhealthy eating). Crucially, social determinants of health can affect mental health outcomes, thereby influencing the management and self-care of T1D. There is also a need for research to explore the integration of diabetes care across various settings and communities to enable continuous support beyond clinical environments. Personalized treatment plans need to account for person-reported outcomes (PRO) and person reported experience measures (PREM) and tailoring to individual needs and preferences are essential in achieving optimal outcomes for patients with T1D.

e. Importance of real-world evidence

Research on T1D using real-world evidence is crucial in advancing our understanding and management of this complex condition. Real-world evidence provides invaluable insights into the diverse experiences and outcomes of individuals living with T1D in everyday settings, beyond controlled clinical trials. By analysing real-world data, researchers can uncover trends, patterns, and factors influencing disease progression, treatment efficacy, and patient outcomes, leading to more personalized and effective interventions. Understanding how different therapies, lifestyle factors, and environmental influences impact individuals with T1D in real-world scenarios allows for the development of more tailored treatment approaches. Moreover, real-world evidence facilitates the identification of unmet needs, disparities in healthcare access, and barriers to optimal disease management, guiding policymakers and healthcare providers in addressing these challenges.

Future research on T1D heavily relies on real-world evidence to validate findings from controlled studies and translate them into real-world practice. Incorporating real-world data into research methodologies enhances the relevance, applicability, and generalizability of study findings, ultimately improving clinical decision-making and patient outcomes. Additionally, real-world evidence fosters collaboration between researchers, healthcare providers, and patients, thereby promoting patient-centred research initiatives and ensuring that research priorities align with the needs and preferences of individuals living with T1D, ultimately improving the quality of life for individuals affected by this chronic condition.

2.3. Complications

a. Basic research on complications

People living with T1D still face a dramatically higher mortality than their peers even when they achieve target glucose range and haemoglobin A1c. This is mostly driven by the higher incidence of cardiovascular events whose mechanisms are still partially unexplained that remains unabated by an optimized glucose control. In the younger ages, T1D has been shown to impact the neurodevelopmental trajectory, even in presence of near-to-normal glucose control. Hyperglycaemia has long been seen as the only driver of diabetes-associated complications, however there is growing evidence for a role of autoimmunity itself and other non-glucose associated mechanisms that may contribute to the higher risk for comorbidities and complications observed in people living with diabetes. Since people with T1D are not protected from the obesity pandemic, leading to increases in the average BMI, combined with evidence that relevant insulin resistance is present at baseline, it is worth exploring whether insulin resistance is an important contributor to the increased cardiovascular risk.

b. Novel therapies: Adjunct therapies, novel insulins, and administration routes

Subcutaneous insulin administration is responsible for chronic peripheral hyperinsulinemia, that in turn may increase insulin resistance and play a role in long term complications. The growing prevalence of obesity also in people with T1D represents an additional determinant of long-term complications. To this end, exploring existing adjunctive non-insulin treatments able to lower daily insulin requirements and to target cardiovascular risk is mandatory as well as developing new treatment targeting T1D-specific mechanisms associated to higher morbidity and mortality. Alternative routes for insulin administration (e.g., inhaled, transdermal or implanted devices) that may reduce the exposure to chronic hyperinsulinemia and represent an additional step towards more physiologic care for those living with diabetes.

2.4. Cure

a. ß-cell protection and ß-cell regeneration

Novel therapies targeting beta-cell regeneration or protecting remaining beta-cells are emerging. However, we need to better understand the effect of potential treatments on the human beta-cell, rather than relying on rodent models . Emphasis should be put on in vitro models of human cells and human data to understand the potential of these therapies. Efforts should be madeto attract intervention trials with these novel agents to European centres of expertise and combine these with interventions using other disease modifying therapies (see above).

b. Stem cell research to preserve beta cell function- Novel beta cell transplantation approaches

Stem cell research holds the promise of generating insulin-producing beta cells from stem cells that can potentially be transplanted into patients to restore insulin production. To protect beta cells from immune rejection new encapsulation techniques are also being developed (ref). These involvebeta-cells encapsulated in a barrier that would prevent them from immune attack and still allow nutrients and insulin to pass through. Some researchers are also focussing on reprogramming other cell types within the body into insulin producing beta-cells. This approach could eliminate the need for transplantation by regenerating insulin producing cells within the patient.

c. Gene therapies

Gene therapies for reinstituting basal insulin production and managing postprandial hyperglycaemia were tested in animal models. Some gene therapy approaches with longer follow-ups in animal models are being prepared for “first-in-human” clinical trials. Genetically modified cell therapies are also being developed with promising initial results. Further research in these gene therapies is needed to progress care for people living with diabetes.

Sustainable research priorities

Along with health care innovation, sustainability must be integrated into research priorities in T1D to ensure that advancements in care and treatment align with environmental responsibility. As we strive to develop innovative therapies and technologies to improve patient outcomes, it is imperative to consider the environmental impact of our actions. This entails adopting sustainable practices throughout the research process, from the design and manufacturing of medical devices to the disposal of pharmaceutical waste. By prioritizing eco-friendly materials, energy-efficient practices, and responsible waste management, researchers can minimize the carbon footprint of T1D research and contribute to a healthier planet for future generations.

3. Type 1 Diabetes Management and Treatment: Anticipated impact of future research

Research within the area of T1D has been rapidly evolving, and keeping T1D research priorities in the agenda promises a future where early detection, personalized therapies, and innovative technologies will transform patient care. By unravelling the genetic and pathogenic complexities of T1D, we can develop targeted interventions and prevent major complications of the disease. Advanced screening

tools will ensure timely diagnosis, enabling prompt and potentially earlier intervention and improved outcomes.

Moreover, the advent of wearable technology and automated insulin delivery systems empowers individuals with T1D to manage their condition more effectively, minimizing the risk of complications and enhancing quality of life. Integration of software and machine learning enhances treatment precision, while novel therapies address individualized needs and promote equitable access to care.

Furthermore, ongoing research into T1D complications and cure strategies offers hope for a future where the consideration of real-world evidence and PRO will significantly reduce burden of the disease. Leveraging real-world evidence in T1D research is indispensable for advancing knowledge, enhancing treatment strategies, reducing healthcare disparities, and ultimately improvie the quality of life for individuals affected by this chronic condition.

Stem cell research and beta-cell protection strategies hold promise for achieving long-term remission or even a cure, transforming the lives of millions affected by T1D.

In summary, the research prioritization in T1D anticipates a future where personalized care, innovative technologies, and breakthrough therapies converge to improve patient outcomes and emerge in a new era of hope and possibility for those living with the condition.

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Endocompass DOMN - Hyperinsulinism (HI) Chapter

[redacted]

Introduction

Congenital hyperinsulinism (HI) is a rare disease of insulin excess associated with severe and recurrent hypoglycaemia, whichcauses neuroglycopaenia with life-long neurodisability in about half of patients. HI is a heterogeneous disease with an identified genetic aetiology in 50% [1]. In many patients, the cause and mechanism of illness remains unknown. Treatment options are limited, with diazoxide being the only medication approved by FDA and second line treatment with somatostatin analogues often complicated by side effects. Patients with diffuse forms of HI with involvement of the whole pancreas, are often unresponsive to standard medical therapies and require subtotal pancreatectomy [2]. Inevitably they develop hyperglycaemia although alternating with episodic hypogycaemia, progressing to diabetes in teenage years [3]. In contrast, the treatment of the focal form of HI representing a solitary region of hyperfunctioning pancreatic tissue and localized by isotope imaging, represents a revolution in translational research with long term cure from hypoglycaemia in the majority [4]. However, significant information gaps remain in our current understanding of illness pathology, mechanism of disease, early identification, monitoring, diagnostic capacity and treatment efficacy. It is not surprising that children, young people and families living with HI face many challenges [5]. Therefore, research prioritisation highlighting specific unmet needs is urgently required to advance the clinical management of HI with improved diagnostics and effective treatment to improve the outcomes for patients and their families.

Subtopic

1. **Diagnostics**

1.1 Newborn Screening

Gap: no newborn screening tool to identify neonates with HI

Research Question: developing a newborn screening tool for HI

Justification: missed or delayed diagnosis of neonatal HI leads to neurodevelopmental delay [Banerjee et al, Orphanet J Rar Dis 22; Stanley C et al Front Pediatr 23]

Types of Studies: biomarker efficacy/validity studies, simulation models, screening pilot

Methods: biomarker panel development, rapid screening for analytes, rapid gene panel screening, selected population pilot, qualitative feedback

1.2 Glucose as a vital sign

Gap: No clear definition of depth, range and extent of hypoglycaemia

Research Question: define hypoglycaemia and severity of hypoglycaemia in the context of HI and long-term patient outcomes

Justification: a clear definition of hypoglycaemia will lead to better identification of HI for treatment. Improved definition and thresholds for depth and duration of hypoglycaemia in glucose profiles will improve research outcomes and treatment goals [Roeper M Front Endocrinol 23]

Types of Studies: cohort studies investigating biomarker status correlating with severity and duration of hypoglycaemia, natural history studies examining glucose profiles and neurodevelopmental outcomes, Continuous Glucose Monitoring (CGM) dataset review

Methods: biomarker development, omics approaches correlating with biochemical phenotype, Cross sectional/longitudinal analysis of glycaemic information in patient/clinician reported databases, CGM data review, prospective CGM trials, clinical trial outcome review

1.3 Glucose monitoring

Gap: Standard of care glucose monitoring by infrequent blood glucose testing results in missed episodes of hypoglycaemia; research evidence for CGM replacing blood glucose testing is incomplete

Research Question: Improved glucose monitoring and interpretation to translate to clinical practice

Justification: CGM profiling requires robust evidence base and guidelines for effective use; present generation of CGM sensors require improvement, adaptation to hypoglycaemia and demonstration of accuracy and efficacy [Win M JCEM 22; Worth C Digit Health 23]

Types of studies: Hypoglycaemia specific sensor development, CGM dataset review, trials of CGM as a therapeutic Management tool, qualitative study involving families and patients

Methods: sensor and algorithm technology development, observational studies testing hypoglycaemia specific CGM sensors/algorithms, artificial intelligence analysis of CGM datasets, clinical trials of CGM efficacy to reduce hypoglycaemia, qualitative studies with patient feedback

1.4 Pancreatic imaging

Gap: Current methods using radionucleotide imaging are restricted to a few centres and limited by cost and set up requirements

Research Question: development of accurate and improved imaging of pancreas to identify focal lesions and exclude diffuse HI

Justification: current methods are cumbersome and expensive, require expertise to produce high quality consistent reports [States L Pediatr Radiol 22]

Types of Studies: radiopharmaceutical development, clinical trials, new imaging technologies

Methods: novel radiochemistry, technology assisted design, innovative trial design minimising radiation exposure

1.5 Genetic testing

Gap: up to 50% cases of persistent HI do not have an identified genetic aetiology; genetic understanding is crucial to understanding natural history, counselling and treatment choices

Research Question: novel genetic aetiology, gene modifications and adaptations, genetic mechanisms of HI, natural history phenotyping for genotype

Justification: understanding of genetic association and causation may predict disease course and treatment response, HI gene panel screening in pilot phase, potential for stem cell therapeutic strategies to reconstruct artificial pancreas, longitudinal phenotype of genetic HI not well known [Rosenfeld E Am J Med Gent 19, Hewat TI, Front Endocrinol 22]

Types of Studies: genome sequencing studies, continuous review and interpretation of gene variants, genotype-phenotype correlations, post genome mechanistic studies, designing and testing cellular chaperone constructs, stem cell development studies, natural history studies

Methods: multi-omics studies, single cell RNA, long read sequencing, gene replication studies in animal models, chaperone protein development, bioresource/tissue bank utilisation studies, bioinformatics, universal genetic database development, reference natural history repositories

2. Medical and Surgical treatment

2.1 Pathogenesis of neuroglycopaenia

Gap: the impact of hypoglycaemia due to HI in the brain is not fully understood

Research Question: developing tools to understand brain impact from hypoglycaemia in HI

Justification: It is important to understand pathways in hypoglycaemia to prevent and treat neuronal injury; neuroglycopaenia has adverse impact with life-long neurodisability in HI patients [Lord K JCEM 15, Avatapalle HB Front Endocrinol 13]

Types of Studies: animal experiments to define hypoglycaemic neuronal injury, gene expression studies to define neuroglycopaenia pathways, design of biomarkers of neuronal injury, imaging, cohort studies, natural history studies, drug target identification to ameliorate neuroglycopaenic injury

Methods: animal brain simulation experiments, single cell RNA profiling, neurophysiological studies, advanced imaging studies, investigation of natural history repositories, artificial intelligence review of drug libraries to reverse neuronal injury

2.2 Drug design and repurposing

Gap: Paucity of drugs to treat HI

Research Question: Design new drugs and repurpose existing therapies for use in HI. Design gene therapy constructs targeting specific mutations. Improve medical management in patients undergoing subtotal pancreatectomy and evolving diabetes

Justification: Few drugs available for treatment of HI; pipelines of development are long/expensive, hence need for repurposing. Specific genetic modification/gene therapies are not currently available and not feasible given the wide range of genetic aetiologies. Management of post pancreatectomy diabetes is suboptimal with occurrence of both hypo and hyperglycaemia throughout childhood, with insulin dependence in teenage years [Banerjee et al, Orphanet J Rar Dis 22]

Types of Studies: drug development targeting various insulin production/release pathways, genotype specific drug design, clinical trials, artificial intelligence-based interrogation of drug libraries for repurposing, development of stem cell technologies, insulin infusion technologies, gene editing, vector constructs, real-world studies of newly developed and repurposed therapies, bihormonal artificial pancreas algorithm development

Methods: physical chemistry, drug design and development, innovative study design and trials, stem cell studies, gene therapy development studies, real-world studies, trial design, artificial pancreas trials

2.3 Improved surgical techniques

Gap: pancreatic surgical techniques are not refined and rely on surgical skill without assistance from technology

Research Question: To develop surgical techniques that limit structural injury and minimise extent of surgery. Precision localisation of focal lesion/boundaries of lesion will retain pancreatic tissue and minimise long-term side effects. Integrating imaging, biomarkers and robotic techniques to aid and assist surgeons for safety and efficacy. Surgical training

through virtual/augmented reality to ensure retention of skill sets for future generations of surgeons

Justification: conservation of surgical skills may be problematic with decreasing emphasis on subtotal pancreatectomy. Tissue sparing surgery is important to delay development of diabetes/minimise side effects. Imaging and robotic techniques could have real-time application during surgery, while virtual reality (VR)/augmented reality (AR)could reinforce skills training [Lord K JCEM 15, Banerjee I Orphanet J Rar Dis 22]

Types of Studies: improvement in imaging techniques, cohort studies assessing surgical choices, natural history studies, quality of life studies

Methods: imaging technology, robotic surgery instrumentations, VR/AR assisted surgical skills acquisition, natural history review

3. Clinical Trials/Industry

3.1 Design of real-world studies and clinical trials

Gap: novel therapies to treat and prevent hypoglycaemia are limited, present therapies are complicated by inadequate efficacy and excess side effects

Research Question: To repurpose existing drug libraries to improve therapy choices in HI; designing new medications with limited side effect profile; developing small molecules for oral therapies

Justification: there is significant patient need to reduce burden of recurrent hypoglycaemia impacting on the brain. Few drugs have been developed over the last 20 years. Current therapies are not significantly effective in a high proportion and therapies are often complicated by side effects [De Leon DD Horm Res 23, Banerjee I Orphanet J Rar Dis 22]

Types of Studies: preclinical studies, phase 1-3 studies, pharmacovigilance studies, choice of therapy outcome studies, observational cohort studies, randomised blinded clinical trials,

Methods: cell and animal models, drug design and development, clinical trials, real-world studies, quality of life assessment, qualitative patient feedback

1. long-term. Research in HI Transition is expected to focus on improvement of varying nature of illness, along with patient perceptions and feedback.

References

Introduction -

1 PMID: 37454648

2 PMID: 30343978

3 PMID: 22190679

4 PMID: 16380471

5 PMID: 35183224

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