Hormone Research in Paediatrics

Review Article

Horm Res Paediatr 2025;98(suppl 2):60–90
DOI: 10.1159/000549194

Published online: November 26, 2025

EndoCompass Project: Research Roadmap for Diabetes, Obesity, and Metabolism

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Keywords
EndoCompass · Diabetes · Obesity · Funding · Roadmap

Abstract
Background: Endocrine science remains underrepresented in European Union research programmes despite the fundamental role of hormone health in human well-being. Analysis of the CORDIS database reveals a persistent gap between the societal impact of endocrine disorders and their research prioritization. At the national funding level, endocrine societies report limited or little attention of national research funding towards endocrinology. The EndoCompass project – a joint initiative between the European Society of Endocrinology and the European Society of Paediatric Endocrinology, aimed to identify and promote strategic research priorities in endocrine science to address critical hormone-related health challenges. ***Methods:*** Research priorities were established through comprehensive analysis of the EU CORDIS database covering the Horizon 2020 framework period (2014–2020). Expert consultation was conducted to identify key research priorities, followed by broader stakeholder engagement including society members and patient advocacy groups. ***Results:*** Research priorities include genetic/epigenetic factors, brain-periphery communication, and environmental influences. Key therapeutic areas include innovative approaches for monogenic disorders, incretin mimetics, dual receptor agonists, microbiome analysis, and improved behavioural interventions. For type 1 diabetes, priorities focus on early detection, insulin delivery systems, and disease-modifying therapies. ***Conclusions:*** This component of the EndoCompass project provides an evidence-based roadmap for strategic research investment. This framework identifies crucial investigation areas into diabetes and obesity pathophysiology, prevention, and treatment strategies, ultimately aimed at reducing the burden of metabolic disorders on individuals and society. The findings support the broader EndoCompass objective of aligning research funding with areas of highest potential impact on endocrine health.

Mechanisms of Obesity and T2D: Monogenic Diabetes

Current State of the Art

Monogenic diabetes, caused by single gene mutations, represents between 1% and 4% of all cases of diabetes in infants and young adults. It is still underdiagnosed, and patients are often misidentified as having type 1 diabetes (T1D) or type 2 diabetes (T2D), hindering appropriate therapeutic management and worsening their prognosis.

Future Research Priorities and Anticipated Impact

Future improvements in monogenic diabetes require a focused research approach encompassing the following different aspects.

Better Awareness and Diagnosis

Limited awareness of monogenic diabetes among healthcare providers significantly hinders accurate diagnosis. This challenge is exacerbated by 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 have steadily led to an increase in the diagnosis rate in the last decade [1].

The creation of a pan-European monogenic diabetes registry, combining 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 American Diabetes Association/

European Association for the Study of Diabetes Precision Diabetes Medicine Initiative provided recommendations on whom and how to test for monogenic diabetes [2]. It also identified open research challenges, such as the urgent need for sequencing data for monogenic diabetes genes from diverse populations.

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 identify effective therapies tailored to individual genetic profiles [3].

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 [4].

Mechanisms of Obesity and T2D: Genetics and Epigenetics

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 heritability of body mass index (BMI) can reach 40–70%. Over 1,000 variants of gene loci, including single-nucleotide polymorphisms (SNPs), are significantly associated with obesity.

Obesity is a chronic disease characterized by excess or dysfunctional body fat that presents risk health. Genes regulate weight across the whole spectrum. In particular, early-onset, severe obesity is strongly driven by genetic factors. Genetic discoveries in mice and in humans identified leptin and the leptin-melanocortin 4 receptor (MC4R) pathway that regulates body weight.

Recent findings show complex central nervous system involvement 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) increases the risk of development of common obesity.

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 to be the cause of obesity.

Epigenome-wide analyses demonstrate the correlation of DNA methylation with clinical features of obesity [5]. 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 [6, 7]. However, further epigenetic modifications can be involved as risk factors in the development of obesity (e.g., post-translational 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 [8] and for a paternal impact on offspring epigenetic modifications. Relevant evidence exists regarding genetic imprinting in the foetus and in the first years of life, related to the development of obesity [9]. Knowledge of epigenetic mechanisms related to obesity and T2D could be the key to developing strategies to prevent and treat diseases.

Future Research Priorities

There is a significant number of:

1. Patients with obesity where there is suspicion of a genetic or epigenetic cause but an unknown gene variant or epigenetic variation.
2. Patients with a genetic diagnosis but an unknown mechanism of disease.
3. Patients suffering from a defined rare form of obesity, where there is limited understanding of the 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, including non-coding genome and epigenome, and innovative bioinformatics tools, to improve efficacy of genetic diagnosis for rare diseases.
2. Elucidate molecular pathomechanisms and define key drivers/pathways of disease by complementing genomics with innovative multiomics integration, including single-cell transcriptomics, proteomics, metabolomics, and epigenetics.

3. Validate identified targets in state-of-the-art, patient-derived disease models (induced pluripotent stem cell- 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 alterations in DNA methylation 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 could theoretically result from additional molecular abnormalities (mutations in other genes, changes in the non-coding region, epigenetic modifications, etc.). Examples include siblings with Bardet-Biedl syndrome with a divergent phenotype, or monozygotic twins, of whom only 1 developed features of ROHHAD (rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation) [10].

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 (next-generation sequencing) has made it possible to detect many genome changes (within the coding and non-coding regions) whose clinical significance is unknown, referred to as variants of uncertain significance (VUSs). The development of collaborative consortiums addressing existing clinical evidence and even performing functional analyses of VUSs could allow for their reclassification, resulting in more accurate diagnoses and patient treatments [11].

There is a need to develop databases of variants detected in genes that could be related to obesity, as well as related tools and software that make use of artificial intelligence and machine learning to improve the theoretical analysis of changes that are discovered. A dedicated website has been created to collect valuable information regarding the most common cause of monogenic obesity, which relates to mutations in the *MC4R* gene (https://www.mc4r.org.uk/). Similar initiatives concerning other genes related to obesity are worth consideration.

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. In this way, the list of genes that are potentially involved in monogenic obesity, in addition to those that are already known (mainly in the leptin-MC4R pathway and in dysmorphic syndromes), can be expanded using comparative whole exome sequencing analysis of patients with singularly severe or particular forms of obesity. The registry 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, and pharmacological treatment). Therefore, increased knowledge of responsiveness to treatment options, in combination with detailed information about genetic/epigenetic signatures, will allow selection of the best individual treatment combination.

Anticipated Impact of Future Research

Understanding the genetic/epigenetic and pathophysiological causes of rare genetic forms of obesity will pave the way for better insights into 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 provide the basis for the development of mechanism-based pharmacological interventions. It will also support the development of future screening programmes, opening the way for early prevention of acquisition of excess body fat.

Mechanisms of Obesity and T2D: Brain-Periphery Communication

Current State of the Art

Obesity is characterized by disturbed energy homoeostasis 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 the 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, the immune system, and the gut. These signals are mainly transmitted by hormonal pathways, such as glucagon-like peptide-1 (GLP-1), ghrelin, leptin, and insulin, and by neural (vagal) routes to the brain. In particular, the gut-brain axis is emerging as a central regulator of energy balance, appetite, and metabolism [12]. Dysregulation within these intricate networks can lead to impaired appetite control, overeating, and disruptions in energy homoeostasis, contributing to obesity and metabolic disorders such as 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 pro-opiomelanocortin (POMC)-expressing neurones in the hypothalamic arcuate nucleus [13, 14]. 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 the enteroendocrine cells (EECs) of the stomach, stimulating food intake by activation of agouti-related peptide (AgRP)- and neuropeptide Y-producing neurones in the arcuate nucleus, while also acting peripherally via afferent vagal activity [15].

Enteroendocrine Cells

Enteroendocrine cells, though only accounting for 1% of gastrointestinal epithelial cells, make the gut the largest endocrine organ [15]. In the distal intestine, EECs secrete anorectic hormones, such as GLP-1, glucose-dependent insulinotrophic peptide (GIP), peptide YY (PYY), and cholecystokinin (CCK). These hormones contribute to gut-brain communication by transmitting signals regarding nutritional status to the brain, affecting energy balance, appetite, and the reward system. [15–20].

Gut Microbiota

The gut microbiome has been identified as an important factor in obesity [16, 21]. Some gut bacteria have been identified as modifying 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, which induced a greater weight gain than bacteria from lean mice [22].

Neural Pathways and Brain Regions

The vagus nerve serves as a crucial link between the gut and the brain, mainly the hypothalamus [17, 23, 24]. The arcuate nucleus plays a critical role in regulating energy and glucose homoeostasis by integrating signals from peripheral hormones to manage calorie intake, glucose metabolism, and energy expenditure [25]. Within the arcuate nucleus, POMC neurones inhibit feeding, while AgRP neurones promote hunger. These neurones 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.

Future Research Priorities

Leptin and Ghrelin Dysregulation

In obesity, 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 [26, 27]. Further research that targets the molecular mechanisms behind leptin and ghrelin dysregulation, particularly within the central nervous system, is crucial for the development of effective therapeutic strategies for obesity and T2D. Research into the specific brain regions that interact with leptin, ghrelin, and hunger signalling will enhance our understanding of how leptin and ghrelin dysregulation contributes to obesity and metabolic complications. Also, more research is needed into potential targeted treatment options in the context of leptin/ghrelin.

EECs as Therapeutic Targets

Targeting EECs and their hormones has become a focus for therapeutic strategies in obesity and T2D [15, 17]. Further research is needed to explore EEC signalling dynamics and how different nutrients and metabolic states (such as fasting or caloric restriction) influence hormone secretion from EECs. Understanding how key hormones (including ghrelin, GLP-1, PYY, and GIP) respond to changes in diet or energy balance will help clarify their roles 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 (e.g., GLP-1 receptor agonists) have already shown promise in managing obesity and T2D. Further research into regulating other EEC hormones, such as PYY and CCK, could enhance our ability to treat metabolic diseases.

Gut Microbiota and Hormonal Regulation

The focus of recent studies has been directed towards the gut microbiome not only changing with metabolic disorders but also being causally involved [17, 28, 29]. Given the key role of the gut microbiota in modulating appetite, energy homoeostasis, and metabolism, it is not surprising 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 is needed into understanding how the gut microbiota influences the production and function of key gut hormones, including GLP-1, PYY, and ghrelin. New data on these interactions are required to uncover how shifts in microbiome may drive hormonal imbalances, and promote obesity and metabolic disorders. In parallel, microbiome-based therapies offer a promising approach towards addressing these issues [30, 31]. Manipulating the gut microbiome – through probiotics, prebiotics, or other interventions – could enhance the effectiveness of hormonal therapies and improve gut-brain communication.

Despite the identification of specific dietary factors altering the microbiome, more intensive investigation is needed to draw clear conclusions and make dietary suggestions. The pathobiological importance of short-chain fatty acid generation is attracting increasing attention. This regulates intestinal physiology, immune function, inflammation, and paracrine signalling, acting both directly in the hypothalamus and indirectly by release of the anorectic gut hormones PYY and GLP-1 [21, 32, 33]. However, more research is needed in this field. In addition, GLP-1 treatment and bariatric surgery have been shown to change the gut microbial composition to a profile similar to that observed in lean subjects [22, 34, 35], 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 include investigating the specific mechanisms by which POMC and AgRP neurones influence the activity of their downstream targets. Exploring how alterations in the melanocortin pathway contribute to obesity and metabolic disorders will be crucial. Studies should also focus on the effects of environmental factors, including diet and stress, on melanocortin signalling, as well as the potential for therapeutic interventions targeting this pathway to restore energy homoeostasis in individuals with obesity. Another key question is how prominent neuronal centres 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 (e.g., the gustatory and olfactory systems).

In-depth phenotyping, with a focus on neurocognitive functions (such as inhibitory control), interoceptive impairments, and food-related brain networks in selected subsamples using functional magnetic resonance imaging (fMRI), will provide a foundation for understanding etiological mechanisms as well as identifying neurocognitive and behavioural 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 [36]. It will become possible to map human WAT adipocyte heterogeneity by means of combined, spatially resolved, transcriptional profiling with single-cell RNA sequencing and image analyses.

The impact of common metabolic disorders such as T2D on WAT microarchitecture and the proportions 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 notable 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 T2D and other metabolic comorbidities associated with obesity. 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 T2D development from childhood to adulthood should be studied. This would include examining the determinants of the onset of insulin resistance and "prediabetic" conditions (singularly altered

glucose tolerance) and their progression to T2D, along with consideration of different profiles among patients with T2D.

Anticipated Impact of Future Research

The anticipated impact of future research on brain-periphery crosstalk and 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 enhanced 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.

Mechanisms of Obesity and T2D: Environmental Factors

Current State of the Art

Obesity emerges based on individual predisposition (genetic and epigenetic factors) and a complex interaction with environmental factors. The preconception and prenatal periods seem 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 quality of life of children and adolescents.

Recognizing the prenatal phase and early childhood as critical windows for the development of persistent obesity and subsequent progressive metabolic dysfunction highlights the importance of disentangling contributing factors to enable individual risk prediction and to uncover the mechanisms driving early metabolic decline. The development of obesity is driven by a complex interaction between genetics and environmental factors, and the brain's regulation of food intake and energy balance. In addition to traditional risk factors, new risks related to environmental factors have emerged.

Future Research Priorities

Childhood

The major challenge is the complexity of the environmental context, the so-called exposome, comprising a multitude of factors that have an impact, including psychosocial, chemical, geophysical, and biological factors, health conditions, and health-related behaviour. Imbalanced responses or maladaptation to changing environmental challenges can impose profound and sustained effects on the developing organism, with a particular impact during vulnerable developmental windows. These exposures act simultaneously via distinct and/or shared mechanistic pathways during susceptible phases of child development, such as the pre- and perinatal periods.

An overall research aim is to identify biological, psychosocial, and behavioural 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 a comprehensive understanding of aetiology 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 patients who are at high risk. Using 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 [37]. Increased consumption of high-calorie, processed foods, such as fast food, sugary drinks, and snacks, is prevalent. In addition, developing countries experience rapid economic transition that shifts dietary patterns from traditional diets to Western-style diets, high in fats and sugars.

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

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 behavioural treatment that specifically addresses satiety responsiveness, as monitored by

functional magnetic resonance imaging, will help children and families better implement behaviour change and be more successful in treatment [38].

Behaviour and Sedentary Lifestyles

The prevalence of obesity is exacerbated by reduced physical activity due to various environmental factors [39, 40]. Increasing sedentary behaviour 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 televisions. 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 affecting 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 [41, 42]. 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 [43]. Ongoing stress affects the hypothalamic-pituitary-adrenal axis, leading to disrupted cortisol levels and cravings for high-calorie foods [44]. Emotional eating (e.g., binge eating) is another important area where targeted intervention strategies are needed [45].

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 [46, 47]. Recent research suggests that exposure to air pollution may be linked to obesity through inflammatory responses and metabolic disruption. 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, such as bisphenol A and phthalates, are commonly found in plastics, personal care products, and food packaging. These substances have been shown to interfere with hormonal systems, potentially contributing to obesity by altering metabolism and fat storage [48–50]. They 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 the identification of 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 behaviours and energy expenditure are essential to develop targeted interventions that promote healthier lifestyles and dietary habits. This holistic approach to understanding and preventing obesity and T2D is necessary for the development of comprehensive strategies that not only address individual behaviours but also reshape the environments that contribute to these widespread health issues.

Therapies in Obesity and T2D: Obesity Pharmacotherapy

Current State of the Art

Obesity is recognized as a chronic disease and a major global health challenge [51]. 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 mean body weight reductions of −9.2%, −8%, and −5.6%, respectively [52]. Setmelanotide is used in some cases of syndromic or hypothalamic obesity [53]. Over the past decade, 3 receptors have stood out as key therapeutic targets for obesity treatment: the GLP-1 receptor, the GIP receptor, and the glucagon receptor.

Future Research Priorities

Exploring (and Exploiting) the Universe of GLP-1, GIP, and Glucagon

Novel anti-obesity medications that exploit these gut hormone 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 [54], while tirzepatide, a dual GIP and GLP-1 receptor agonist, achieves an impressive weight loss of – 20.9% [55]. This makes them currently the most potent weight loss drugs on the market. Retatrutide, a triple GLP-1, GIP, and glucagon agonist, is currently undergoing phase 3 clinical trials. It has been shown to reach, at a maximum dose, a mean weight loss of −24.2% at 48 weeks [56]. These medications are all in injectable form.

The hormone GIP, like GLP-1, stimulates glucose-dependent insulin secretion and decreases appetite. In T2D, GIP secretion is preserved, but its insulinotrophic action is reduced [57]. It carries a protective effect against GLP-1-induced nausea and has a role in lipid deposition and lipogenesis [58]. It is particularly fascinating that GIP antagonism, like GIP agonism, is linked to weight loss, via mechanisms that are not completely clear. An investigational drug that combines GIP receptor antagonist and GLP-1 receptor agonist activities is undergoing phase 2 trials [59].

Glucagon agonism reduces food intake, triggers lipolysis, and seems to increase energy expenditure [60]. Glucagon can also activate the GLP-1 receptor on β-cells, stimulating insulin secretion in a paracrine way [60], while combination with GLP-1 and/or GIP receptor agonists protects against glucagon-induced hyperglycaemia. Survodutide and mazdutide are GLP-1 receptor agonists combined with a glucagon receptor agonist and are currently undergoing phase 3 trials.

Regarding the oral route, oral semaglutide, which has been available for some years for treatment of T2D at a different dosage, has completed phase 3 trials for an obesity indication, showing a mean weight loss of −17.4% [61] Orforglipron is an oral, partial GLP-1 receptor agonist, which is biased towards G-protein activation over β-arrestin recruitment at the GLP-1 receptor, and is undergoing phase 3 trials for the treatment of obesity treatment [62].

Other Gut Hormone 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 [63]. Cagrilintide, an amylin analogue, in combination with semaglutide (CagriSema), is undergoing phase 3 trials. The addition of amylin agonism to GLP-1 receptor agonism seems to produce a favourable effect on weight loss in diabetes [64], which notoriously is a condition where obesity is more difficult to tackle.

Besides GLP-1, studies have shown that GLP-2 is also involved in β-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 receptor agonists in double agonists (dapiglutide) that are currently undergoing phase 2 trials for obesity [65, 66].

Thinking outside the Gut

In addition to gut hormone analogues and antagonists, other medications that exploit different mechanisms could be on the horizon. These include bimagrumab, an intravenously administered monoclonal antibody directed against the activin type 2 receptor, which stimulates skeletal muscle growth and could be of use in sarcopenic obesity [67]. Another potential target is the growth/differentiation factor-15 (GDF-15) receptor. Observations highlighted that elevated, cancer-secreted GDF-15 increases satiety and induces weight loss by acting centrally [68].

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. Preclinical studies have demonstrated that activating various neuronal populations within the dorsal-vagal complex reduces feeding behaviour in rodents [69].

Other Preclinical Therapeutic Targets

Fibroblast growth factor 21 (FGF21) is a cytokine that is induced by a wide range of stress conditions (such as prolonged fasting), and aims to restore metabolic homoeostasis [70]. In obesity, insulin resistance, and fatty liver disease, FGF21 is usually elevated because of an impairment in its signalling. Thus, obesity is considered a state of FGF21 resistance [71]. In addition, FGF21 is involved in dietary preference and appetite, and its levels have been found to rise in response to a hypercaloric carbohydrate- or fat-rich diet [72]. However, FGF21 has 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 [72]. Despite these issues, the magnitude of weight loss observed in preclinical models and our understanding of the mechanisms of FGF21 resistance suggest 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, which was exploited in the early 2000s with rimonabant [73]. Recent advancements have led to the development of new-generation CB1R inverse agonists with significantly reduced brain penetration compared with rimonabant, targeting peripheral CB1R receptors [73, 74]. 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 [73].

Brown adipose tissue (BAT) is another interesting and biologically plausible target for the treatment of obesity. It has the unique feature of generating heat from its own triglyceride content, thanks to the presence and activation of uncoupling protein 1 (UCP1) [75]. However, it has become clear that multiple thermogenic mechanisms exist [76]. It is very likely that thermogenic adipocytes in deep neck adipose tissue use UCP1-dependent and independent pathways for non-shivering thermogenesis [77, 78]. Brown adipose tissue 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 in BAT thermogenic activity) [75].

Many natural and chemical UCP1 activators have been identified [79], and some drugs have been found to induce metabolic activation of BAT. These are mainly sympathomimetic drugs, for example, phentermine, sibutramine, fenfluramine, and peroxisome proliferator-activated receptor-γ agonists, such as pioglitazone, but also TRPV1 and TGR5 agonists [75]. However, no drug thus far, not even the most recent β3-adrenergic agonist mirabegron, has been shown to selectively activate BAT in humans without inducing cardiac chronotropic effects [75].

Anticipated Impact of Future Research

The Future Will Be in Oral Medications

Besides exploring new therapeutic targets, research is also focussing 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 because of the structure of the gastrointestinal tract, which 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 [80].

New-generation oral drugs, such as orforglipron, are called "small-molecule" agonists. That is, they are ligands of the GLP-1 receptor that work via an allosteric mode to partially agonize the receptor [12, 81]. They are biased towards Gαs protein recruitment (favouring cAMP production) over β-arrestin (different from "older" GLP-1 receptor agonists) [82]. Altered receptor engagement leads to retention of the GLP-1 receptor on the cell surface and continued signalling over a prolonged time [83]. This bias, which is thought to also be exploited by tirzepatide [84], ultimately leads to a more robust response and increases the potency of the drug with regard to glycated haemoglobin and weight loss [83].

In contrast to injectable GLP-1 receptor agonists, oral "small-molecule" non-peptide GLP-1 receptor agonists are also easy to manufacture [83]. Given the anticipated high demand for GLP-1 receptor agonist therapy in the future, the potency, simple route of administration, and ease of manufacture of these drugs make them convincing candidates for the treatment of obesity and T2D.

Tailored Pharmacological Treatment Based on Obesity-Related Complications

Obesity is strongly associated with T2D. When these 2 conditions co-exist, patients generally achieve less weight loss compared with those without diabetes. For example, in clinical trials, weight loss at 68 weeks with semaglutide 2.4 mg was −9.6% in patients with T2D vs. −14.9 in patients without diabetes, despite similar lifestyle interventions [4, 85]. This highlights the need for even more potent medications to effectively address obesity in patients with obesity and diabetes. Research should also focus on why patients with diabetes are less prone to lose body weight in clinical trials and in real life than patients who are only affected by obesity.

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 receptor agonists alone, despite similar weight loss, due to a direct effect of glucagon on hepatic lipid oxidation [86]. Yet, GLP-1 receptor agonists alone reduce epicardial fat, and semaglutide has been shown to improve physical limitations and symptoms in people with obesity and heart failure with preserved ejection fraction [87]. The dual GLP-1/GIP receptor agonist

tirzepatide has shown convincing evidence for treating OSA in patients with obesity [88].

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.

Past and existing therapeutic clinical trials and research in obesity and T2D usually focus on 1 or 2 complications of the disease. With the advancement of endocrine/medical care, patients with T2D are living longer with multiple target organ complications. For those complex patients with a combination of more than 2 complications, evidence is scarce. The current use of therapeutics for obesity/T2D in the clinical arena for this vulnerable group is based on experts' recommendations (e.g., in clinical practice guidelines). High-quality evidence is required for decision-making in the management of patients with obesity or T2D associated with multiple complications; thus, specific trials are highly recommended.

Key Points

- Novel anti-obesity medications such as semaglutide and tirzepatide have opened a new era in the treatment of obesity and T2D, reaching weight loss of up to 15–21%.
- A plethora of new drugs, which exploit the incretin system receptors (for glucagon, amylin, GLP-2) and/or which specifically target receptors outside the gut (the activin type 2 receptor in muscle, and the calcitonin and GDF-15 receptors in the brain), will become available in the coming years, while research is progressing on other promising targets (FGF21, CB1R, and BAT).
- Future pharmacological therapy of obesity will be less costly and burdensome, possibly in an oral form, and tailored based on obesity-related complications (and patient preferences).

Therapies in Obesity and T2D: Behavioural Modification

Current State of the Art

Behavioural modification (BM) is the central component of lifestyle interventions, which are considered to be the cornerstone approach for the management of obesity and T2D [89, 90]. Pioneer lifestyle intervention trials have included the Look AHEAD study [91] and the Diabetes Prevention Program [92], among others [93, 94]. Their study design placed BM (i.e., strategies) as a key element, combined with diet and physical activity. According to their findings, a significant loss of body weight was associated with benefits in medical and psychosocial outcomes, which is foremost in the prevention and treatment of T2D, at least in the short and intermediate terms [95]. However, despite this, in real-world clinical settings, the implications of lifestyle interventions based on BM are not that significant. It seems that they are not fully or properly delivered in accordance with their real potential in populations with obesity and/or T2D [96, 97].

Future Research Priorities

The discrepancies between the effectiveness of lifestyle interventions based on BM in research settings and their non- or 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 need investigating in future, as follows [96, 97].

Standardization of Lifestyle Interventions Based on BM

According to the literature, the use of the terminology of lifestyle interventions based on BM 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 [98–100]. This has made their success arguable in the management of obesity and T2D [96].

Therefore, first of all, cornerstone research is needed, conducting rigorous "systematic reviews and meta-analyses," from which a consensus can be established on standardized lifestyle interventions based on BM [101]. 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 [89, 102]. 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. The output should also be manual-based, to be fluid in skills transferability, and patient-centred with a self-administered option, so as to meet patients' needs [103]. Therefore, there needs to be a clear description based on a protocol (i.e., personalized but standard in content, duration and procedures). The programme(s) should be properly adaptable for any public health

setting (i.e., foremost primary care) and clinical setting (specialized outpatient and inpatient settings, including mental health and bariatric surgery), as well as useable across different populations (children, adolescents, adults in middle age, and the elderly) and ethnicities [104, 105].

Studies on Effectiveness and Identification of New Strategies

Studies of the effectiveness of lifestyle interventions based on BM should be conducted to improve the programme(s) and enrich it with new behavioural strategies [102]. Moreover, studies that identify new strategies that lead to an increase in adherence to the programme(s), and reduce rates of attrition and dropout, are crucial, especially in the long term, since the beneficial effect of programmes of lifestyle interventions based on BM is not maintained with time [99].

For this reason, the effectiveness of such programmes should also be tested at different clinical settings as well as at different intensities (i.e., durations of programme, numbers of sessions, health professions involved), ways of delivery (e.g., individually or in a group, in-person or through telemedicine or apps), and, last but not the least, in combination with other therapeutic approaches for obesity and T2D, such as anti-obesity/anti-diabetic medications and/or bariatric/metabolic surgery.

Studies on Training and Dissemination

It is extremely important to conduct research on how to improve training in and dissemination of these lifestyle intervention programmes widely among health professionals, as well as their implementation at different levels of clinical setting [106]. With this in mind, research should identify the most effective training modalities and, at the same time, consider the ease of dissemination and deliverability (i.e., to be cost-effective).

To complement this area of research, the professional skills and competence of the healthcare professionals that are delivering these programmes should always be assessed and reviewed for possible improvement, along with how regularly they present the programmes to their patients [107]. Technological advancements cannot be ignored, so 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, without being prevented by logistical obstacles (geographical location, finances, etc.) [108].

Anticipated Impact of Future Research

The anticipated future impact of conducting this research will be to crystallize the concept of BM as a standardized approach, composed of specific procedures, as for any other medical intervention. This will facilitate the task of assessing the approach's effectiveness and render it 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 lifestyle interventions based on BM and their dissemination, especially taking into account strategies for technological advancement, will make these programmes more accessible to a wide range of healthcare professionals through web-training and "dissemination by distance," and more easily accessible for patients through the use of telemedicine and apps.

Therapies in Obesity and T2D: Personalized, Targeted Therapy for Monogenic Disease

Epidemiology, Societal Impact, and Research 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 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 [109, 110]. Mutations in *LEPR* are found in 3–4% of patients with severe obesity [111, 112]. Furthermore, the prevalence of monogenic obesity could reach up to 30% in populations with a high consanguinity [113].

The discovery of these forms of obesity has been pivotal in identifying key mechanisms of appetite control and 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 the discovery of underlying genetic causes of neonatal diabetes, with 82% of cases now having a genetic diagnosis [114]. In 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 caused by an activating mutation in one of the genes encoding the potassium channel can be successfully transitioned off insulin onto oral sulphonylurea treatment, with near normalization of blood sugar [115]. This effect seems to persist in the long term [116]. Patients with MODY due to *HNF1A* and *HNF4A* are exquisitely sensitive to low-dose sulphonylureas. Once again, if they are undergoing insulin treatment, they can often transition off insulin [117]. There remain a number of key challenges – in implementation, discovery, and treatment.

Future Research Priorities: Monogenic Obesity

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

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.

- Further research is necessary to enhance understanding of the impact of lifestyle interventions in monogenic obesity, to tailor treatment more effectively.
- There is an urgent need for more personalized prevention and treatment strategies. Nutritional and exercise genomics or metabolomic evaluations might be useful and beneficial.

Pharmacological Treatment

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

GLP-1 Analogues. Current evidence suggests a maintained efficacy of GLP-1 agonists in genetic obesity characterized by an impaired MC4R pathway. Further studies are needed of the long-term effects of GLP-1 analogues in individuals with *MC4R* mutations. Additionally, it would be of significant interest to explore the effects of GLP-1 analogues in patients with monogenic obesity caused by other mutations.

Leptin. Leptin has been implicated in promoting cancer progression through activation of pro-proliferative or anti-apoptotic pathways [118]. Future studies are essential to establish a causal relationship between leptin treatment and the pathogenesis of obesity-related cancers as a long-term effect.

MC4R Agonists (*Setmelanotide*). The medium- and long-term side effects of setmelanotide should be monitored, especially evaluation of the consequences of chronic stimulation of melanocytes. Although there are some explanations, the variation in weight loss between patients with different mutations in the MC4R pathway emphasizes a further need to understand the mechanisms. Another area of research would examine the potential benefit of MC4R agonists for patients with common polygenic obesity.

Unimolecular Polypharmacology. Dual or triple incretin-based drugs are currently being approved as potential therapies for obesity. There is an emerging need to investigate their effectiveness in specific types of monogenic obesity.

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.

Gene Therapy

Patients with monogenic obesity might benefit from novel treatment technologies.

CRISPR and Gene Editing. Gene-editing technologies have 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 [119]. Future research is needed to focus on delivery methods, off-target effects, and the long-term efficacy and safety of these technologies.

Antisense Oligonucleotides. Antisense oligonucleotides are another promising treatment modality. Despite limitations in crossing the blood-brain barrier, future studies are needed to explore their effectiveness in monogenic obesity.

Bariatric Surgery

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

Future Research Priorities: Monogenic Diabetes

Implementation of Appropriate Testing and Treatment

Global implementation of appropriate testing strategies and subsequent appropriate treatment is essential, to ensure patients benefit from 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 is sub-Saharan Africa. Different strategies are needed in White European populations and other ethnicities, especially when there is a high prevalence of slim young-onset T2D or a high prevalence of consanguinity [120, 121].

Identification of Novel Causes of MODY

There are a considerable number of individuals who have all the characteristics of MODY but do not have the presently defined genetic aetiologies. These instances may reflect genes with reduced penetrance such as *RFX6* [122], a high polygenic burden, or a combination of the 2.

Identification of Novel Causes of Neonatal Diabetes

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 β-cell.

Neurological Deficits due to Potassium Channel Mutations

Improved understanding and therapy are required for neurological deficits due to potassium channel mutations. Work is needed to understand the range of deficit (from mild to severe) that is seen in patients with mutations in the ATP-sensitive potassium channel that result in neonatal diabetes and MODY. For those with severe intellectual impairment, there is some response to sulphonylurea, which needs further investigation. Other therapies that have better brain penetrance should be examined [123–126].

Penetrance of Pathological Mutations

Research is needed to enhance understanding of genetic and non-genetic modifiers that alter the penetrance of pathological mutations in monogenic diabetes. Evidence from almost all subtypes of monogenic factors shows variable penetrance of the same monogenic aetiological variant. This needs to be investigated to see whether there are definable modifiers, such as polygenic risk scores or epigenetic modification during maternal diabetic pregnancy, that alter age of diagnosis by > 10 years [127, 128].

Anticipated Impact of Future Research

Further studies focussing 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 to common forms of obesity and diabetes.

Therapies in Obesity and T2D: Dual Receptor Agonists

Epidemiology, Societal Impact, and Research State of the Art

Agonists of the GLP-1 receptor 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 [129]. The hormone 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-1 and GIP receptors (tirzepatide) or both GLP-1 and glucagon receptors (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% [130, 131]. They do not only enhance insulin secretion and improve glycaemic control, but also mitigate the adverse effects commonly associated with GLP-1 receptor agonists alone. For instance, treatment with a GIP receptor agonist has been shown to protect against nausea and anorexic behaviours in mice [132, 133].

Future Research Priorities

Tissue-Specific Underlying Mechanisms

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 mechanisms still need to be elucidated. Both agonists and antagonists of the GIP receptor have been shown to prevent obesity, as evidenced by studies demonstrating that GIP receptor antagonism can reduce weight gain in mice [134]. These paradoxical, 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 [135].

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 T2D experience greater weight loss with GLP-1/GIP receptor agonist therapy than those with T2D who have similar BMI [130, 131]. Additionally, tirzepatide and cotadutide have shown promise in reducing biomarkers of non-alcoholic steatohepatitis in patients with T2D, indicating potential benefits beyond glycaemic control and weight loss [136]. 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-1 receptor agonists, longer-acting GIP and GLP-1 receptor 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 such as diet and exercise. Additionally, assessing dual agonists in children and adolescents is essential, due to the rising rates of obesity and T2D in younger populations.

Anticipated Impact of Future Research

The recent completion of clinical trials such as SURMOUNT-3 and -4, with SURMOUNT-5 expected to conclude in January 2025, will be crucial in 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 who are struggling with obesity and T2D. 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 such as gradual dose reduction combined with behavioural interventions to mitigate the relapse.

Therapies in Obesity and T2D: Incretin Mimetics

Epidemiology, Societal Impact, and Research State of the Art

Diabetes mellitus represents a global medical, economic, and social problem, due to the high and growing prevalence of disease, and the risk of micro- and macrovascular as well as neurological complications, which lead to significantly increased morbidity, mortality, and economic costs. The International Diabetes Federation Diabetes Atlas reports that 10.5% of the adult population (aged 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, projected to increase to 643 million in 2030. By 2045, it is estimated that 1 in 8 adults, ~783 million people, will be living with diabetes, an increase of 46%.

Over 90% of people with diabetes have T2D, which is driven by socio-economic, demographic, environmental, and genetic factors, including urbanization, an ageing population, decreasing levels of physical activity and increasing prevalence of overweight and obesity. Approximately 80% of patients with T2D have obesity 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 T2D [137].

One of the main research priorities in this area is the development and active implementation of new effective tools to decrease and maintain body weight, addressing the targets related to the pathophysiology of T2D. Recent pharmacologic interventions with incretin derivatives have shown that, by obtaining substantial and sustained weight reduction, a markedly lower risk of progression to T2D is observed than with placebo [138].

Introduction into clinical practice of the new anti-hyperglycaemic medications, the GLP-1 receptor agonists, has led to the significant improvement of diabetes control. This is accompanied by a dramatic decrease in body weight in the majority of cases. Also, most importantly, it has led to a significant reduction in cardiovascular morbidity and mortality, not just in patients with T2D, but also in subjects who have obesity without diabetes.

Such positive actions of this class of medications, the GLP-1 receptor agonists, are attributed to their numerous effects, including:

- increased insulin biosynthesis and improvement of β-cell function,
- reduced insulin resistance,
- decreased hepatic glucose production, lipogenesis in the liver and 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 and diuresis and decreased inflammation and oxidative stress in the kidneys, and

- increased insulin sensitivity in the muscles [139].

In randomized clinical trials in patients with T2D, GLP-1 receptor agonists showed the ability to significantly decrease the risk of myocardial infarction, stroke, and cardiovascular mortality compared with placebo, in addition to standard antihyperglycaemic treatment. In the 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 receptor agonists are not restricted to the reduction of cardiovascular macrovascular complications. Recently, in the FLOW study, semaglutide reduced the risk of progression of kidney disease, as well as death from cardiovascular and kidney disease, by 24% in patients with T2D, when compared with placebo.

In addition, GLP-1 receptor agonists have been shown to be effective in reducing cardiovascular morbidity and mortality in the recent SELECT trial, which enrolled subjects who had obesity without diabetes. Semaglutide reduced the risk of myocardial infarction, stroke, and cardiovascular mortality by 20%.

There are important and exciting data regarding new medications in this area which have dual or even triple mechanisms of action. For instance, tirzepatide, which acts on the GLP-1 and GIP receptors, has shown an even higher potency in reducing body weight. Other medications acting on other incretins are at advanced stages of development. Furthermore, GLP-1 receptor agonists are promising as new tools for the treatment of other diseases, such as metabolic dysfunction-associated liver disease, nephropathies, polycystic ovary syndrome, neurodegenerative diseases (e.g., cognitive impairments and Alzheimer's disease), and cancer, due to the pleiotropic mechanisms of action of these medications.

Future Research Priorities and Anticipated Impact

Further research into incretin mimetics is important in order to maximize the benefits that these drugs can provide in the treatment of T2D and obesity. They have the potential to offer valuable further improvements in patient care and disease management.

Therapies in Obesity and T2D: Microbiome Shotgun Sequencing in Guiding Nutritional Strategy

Epidemiology, Societal Impact, and Research 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; the relationship is symbiotic in a healthy body [140, 141]. Each person has a unique microbiota including bacteria, viruses, fungi, archaea, and protozoa, which can be partially changed under the influence of various factors throughout life. A difference in taxonomy and a higher diversity of gut bacteria have been observed in lean people compared with those with obesity [142].

A 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 the microbiota using different lifestyle and dietary factors. Nutrition, especially dietary fibre, significantly affects the amount and type of gut bacteria [140–142]. Current understanding regarding the connection between genes of the microbiota and nutrition is limited, due to the complicated techniques that have been used for detection of genes in the microbiota [141].

Future Research Priorities

The first aim is to explore the gut microbial profile in people with metabolic diseases (e.g., obesity, metabolic syndrome, and T2D). Metagenomic and metataxonomic strategies should be used to understand the heterogeneity of genes within a species or within a population.

Previous studies of the composition of microbiota 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). This has between 2 and 5 million reads per sample, is non-inferior to DS in terms of functional gene sequencing and taxonomy, and is more cost-effective for large-scale screening studies [143]. 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 [144].

The second research goal is to establish a change in the composition and abundance of the microbiota after different diets (such as the Mediterranean diet, a ketogenic diet and diets with different types and amounts of dietary fibre, etc.) or the use of probiotics. The third objective is to monitor the impact of changes in the

microbiota, after intervention, on metabolic and inflammatory parameters, such as blood glucose, insulin, lipids, high-sensitivity C-reactive protein, interleukin-6, and tumour necrosis factor-α.

Anticipated Impact of Future Research

Analysis of the microbiota using a 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.

Therapies in Obesity and T2D: Next-Generation Sequencing in Guiding Nutritional Strategy

Epidemiology, Societal Impact, and Research State of the Art

The rise in the number of people with chronic metabolic diseases, such as obesity and diabetes, is a serious public health concern globally. Food and nutrition are essential parts of the management of metabolic diseases [145]. Still, there is no consensus on the ideal nutritional strategy and percentages of calories, carbohydrates, proteins, and fats for people with diabetes and obesity [146]. Results from recent human clinical studies have shown that blood glucose levels change differently in different people in response to the same standardized meals [147]. Thus, a 1-size-fits-all approach does not work in a population with diverse genetic backgrounds and dietary practices. The goal of precision nutrition is to provide more precise and dynamic nutritional recommendations than are currently possible through population-wide guidance.

Next-generation sequencing is a powerful tool used in genomics research, providing comprehensive insights into genome structure, genetic variations, gene expression profiles, and epigenetic modifications. This method paved the way for a new era of personalized 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.

Future Research Priorities

Obesity and diabetes are polygenic, 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 a differential response to specific nutrients, relating this variation to various diseases, such as diabetes and obesity [148]. Nutrigenomics explores the interaction between genes and nutrients and their effects on human health, as nutrients up- or downregulate gene expression and, consequently, at the molecular level, metabolic responses [149].

Genome-wide association studies, including a constantly increasing number of individuals and biostatistical meta-analyses of the generated data, are needed to decipher the role and effectiveness of different dietary regimens in individuals with obesity and diabetes. Different polygenic risk scoring approaches need to be developed and optimized, 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 personalized diet [150–152]. There is insufficient evidence demonstrating the superiority of precision nutrition over traditional dietary recommendations, and this needs to be studied.

Therefore personalized nutrition research is needed and should focus on:

- Identification of genetic variants (SNPs) that influence the intake and metabolism of specific nutrients and predict the variability between individuals in response to dietary interventions.
- Identification of genetic variants (SNPs) related to postprandial glucose levels, insulin, and regulation of energy homoeostasis.
- 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 Impact of Future Research

Recent advancements in next-generation sequencing hold great promise for unlocking new insights into genomics and improving the understanding of diseases and personalized healthcare [153]. Identification of a wider spectrum of genetic factors that play a role in the relationship between diet and metabolic disease could lead to a better understanding of the optimal diet for an individual. Personal genetic profiling of metabolism and physiology will, in turn, lead to personalized nutritional recommendations, based on the complex network of

genetic variants that are 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 [154].

Management and Treatment of T1D

Epidemiology, Societal Impact, and Research State of the Art

Type 1 diabetes is the most common metabolic disorder in children. It has a lifelong impact on those affected and their families or caregivers. Over recent decades, a steady rise in the incidence of T1D has been observed [155]. Importantly, this disease still carries a high burden of morbidity and increased risk of (mostly cardiovascular) mortality. Children who develop T1D before 10 years of age lose on average 14–17 years of life expectancy [156].

Type 1 diabetes 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 β-cells within the pancreas. Although T1D predominantly emerges during childhood and adolescence, half of all T1D diagnoses occur beyond the age of 18 years.

Type 1 diabetes is the archetype model of autoimmunity, which is the underlying mechanism of disease, affecting 9 million people worldwide [157]. In Europe, ~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 proportion 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% of children during their initial clinical presentation of T1D [158]. Diabetic ketoacidosis 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 β-cell function, and the duration of exposure to the disease.

On top of the burden T1D places on people living with diabetes and their families, diabetes is an expensive disease, with an important economic impact on healthcare systems. The estimated annual cost of T1D in Europe is more than €30 000 million. Recent work by the Juvenile Diabetes Research Foundation (now Breakthrough T1D) highlighted the potential impact of screening and diagnosis of T1D at preclinical stages on the societal cost of T1D [159]. The cost of treating 1 person living with diabetes over a 25-year period is approximately EUR 100,000–200,000. Indirect costs and the emotional burden need to be considered alongside these direct costs.

While most of those 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 and more barriers to diabetes care among ethnic communities [160]. 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 contributing 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 well-being of individuals and communities [161]. 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 care in T1D, and how to provide social support to people living with diabetes across communities.

Future Research Priorities

The key future research priorities encompass the "4Cs" in T1D management and treatment: concept, care, complications, and cure.

Concept

Disease Pathogenesis and Heterogeneity. European support has been crucial in advancing our knowledge of the pathogenesis of T1D, discovering novel biomarkers, and understanding the heterogeneous character of the disease. Many questions remain regarding the genetic markers of the disease, with the need to improve our genetic predictive power by better understanding the genetic build-up that leads to T1D. Better biomarkers are needed to help predict those who will develop autoimmunity early or later in life and, in particular, biomarkers are needed to predict who will progress from pure autoimmune attack of the β-cell to full blown clinical T1D.

Innovative Health Initiative (IHI)-supported projects, such as INNODIA, have collected samples and multiomics data from hundreds of people with newly diagnosed (stage 3) T1D or at preclinical stages (1 and 2). These biosamples, which have been collected using highly standardized procedures, and data from multiomics analyses of these samples, are available for more in-depth research regarding 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).

Screening and Early Detection of T1D. At present, we screen for genetic risk of T1D by using genetic risk scores, combining human leucocyte antigen and SNPs of different genes. Further refinement of these tools is needed to improve genetic risk screening in the general population.

In parallel, initiatives concerning early (preclinical) diagnosis of T1D are underway, using detection of antibodies in the blood of participants. Further refinement of the assays for these antibodies is needed, to allow upscaling of the initiatives and integration into healthcare systems. Collaboration between academia and industry is of the utmost importance here.

In addition, monitoring tools for those at risk or at a preclinical stage (1 or 2) are to be refined. An IHI project (EDENT1FI) is evaluating different paths to screen and explore the potential of continuous glucose monitoring (CGM) as a monitoring tool. Other methods are needed.

Disease-Modifying Therapies in T1D. A growing insight into the pathogenesis of T1D has brought disease-modifying therapies. However, we need to move on from a 1-size-fits-all approach as heterogeneity in disease trajectories is present and therapies may not work in everyone. Therefore, research is needed into biomarkers of therapeutic effect (both failure and success). Attracting novel disease-modifying therapies to Europe is also of paramount importance.

A network has been created to execute these trials: INNODIA.org. This is a spin-off of the IHI projects INNODIA and INNODIA HARVEST. However, more support is needed to attract these trials to Europe, with emphasis on standardized execution of the trials (using master protocols), combination trials, and research on biomarkers of effect.

Novel Endpoints in Clinical Trials. Staging of T1D relies on 2 tests: measurement of islet autoimmunity and the oral glucose tolerance tests. The latter is moderately invasive and poorly reproducible. As a result, current staging is unable to describe the actual disease heterogeneity, to accurately estimate the risk of disease progression, or to serve as a surrogate endpoint in clinical trials involving disease-modifying treatments.

The need to define pre-symptomatic disease progression across different age groups challenges the current staging paradigm and requires novel, minimally invasive tools that are 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. This limits the feasibility of clinical trials, 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-responders to 1 or more medications. There is a need for reliable surrogate endpoints that are able to track disease progression in clinical trials reflecting actual β-cell function and time to symptomatic disease.

Care

Wearable Technology for Early Detection and Management. Routine glucose monitoring is fundamental to precisely delivering insulin replacement therapy. Based on a substantial number of clinical trials that have validated efficacy and safety, CGM devices represent the current standard of care, regardless of age, diabetes type, stage of the disease, and insulin delivery modality. Use of CGM can transform diabetes care by improving glycaemia, reducing acute and chronic complications, and improving quality of life [162].

The use of CGM-derived metrics, such as time in range, time below range, and time above range, as well as

unified reporting, presentation, and visualization of CGM data, greatly facilitates communication between people with diabetes, their families, and healthcare providers. As CGM devices are becoming more advanced, accurate, and broadly accessible, their usability is expanding beyond the role of insulin-dosing titration guidance, including for non-insulin-treated persons with T2D 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 [163–166]. Finally, CGM is a core component of glucose-responsive automated insulin delivery (AID) systems [167].

Automated Insulin Delivery. Whether integrated into an insulin pump or as a smartphone/tablet/computer application, AID systems consist of a CGM device that feeds glucose data to a control algorithm. This algorithm then translates the real-time data it receives and computes the amount of insulin to be delivered via the insulin pump. The use of AID enables glucose levels to be maintained 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 [168–173]. These observations have also been complemented in real-world settings, underscoring that access to this technology should be made broadly available and based on the needs of each individual.

Software and Machine Learning Approaches. With the exponential increase in data generated by technologies used in diabetes care, machine learning approaches and automated decision support systems might play a crucial role in care of patients, by leveraging extensive quantities of information to enhance disease management, prediction, and treatment personalization [174]. 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 [175]. 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 identify individuals at a higher risk of developing complications, allowing for timely and person-tailored interventions to prevent or mitigate their progression.

Access to Care, Quality of Life, and 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 individuals with 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 consider the risk of diabetes distress and how social relationships are affected, to account for person-reported outcomes, and to be tailored to individual needs and preferences. This is essential in achieving optimal outcomes for individuals with T1D.

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 outcomes in people who are living with diabetes. This can lead 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 outcomes in people living with diabetes. Additionally, real-world evidence fosters collaboration between researchers, healthcare providers, and people living with diabetes, thereby promoting person-centred research initiatives and ensuring that research priorities align with the needs and preferences of individuals who are living with T1D, ultimately improving their quality of life.

Complications

Basic Research on Complications. People living with T1D still face a dramatically higher mortality than their peers, even when they achieve the target range for glucose and glycated haemoglobin. This is mostly driven by the higher incidence of cardiovascular events, the mechanisms of which are still partially unexplained but which remain unabated by optimized glucose control. At younger ages, T1D has been shown to impact the neurodevelopmental trajectory, even in the 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 for other non-glucose associated mechanisms that may contribute to the higher risk of comorbidities and complications that are 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 risk of cardiovascular and other comorbidities.

Adjunct Therapies, Novel Insulins, and Administration Routes. Subcutaneous insulin administration is responsible for chronic peripheral hyperinsulinaemia which, in turn, may increase insulin resistance and play a role in long-term complications. The growing prevalence of obesity in people with T1D represents an additional determinant of long-term complications.

To this end, exploring existing adjunctive non-insulin treatments that are able to lower daily insulin requirements and to target cardiovascular risk is mandatory, as well as developing new treatments targeting T1D-specific mechanisms associated with higher morbidity and mortality. Alternative routes of insulin administration (e.g., inhaled or transdermal routes, or implanted devices) may reduce the exposure to chronic hyperinsulinaemia and represent an additional step towards more physiological care for those living with diabetes.

Cure

β-Cell Protection and Regeneration. Novel therapies are emerging that target β-cell regeneration or protect the β-cell. However, we need to better understand the effects on human β-cells, rather than rodent models (which all too often are used). An emphasis should be put on in vitro models and human data to understand the potential of these therapies. Efforts should be made to attract intervention trials using these novel agents to Europe and to combine these with interventions using disease-modifying therapies (see above).

Stem Cell Research and Novel Approaches to β-Cell Transplantation. Stem cell research holds the promise of generating insulin-producing β-cells, which can potentially be transplanted into individuals to restore insulin production. To protect β-cells from immune rejection, new encapsulation techniques are also being developed. These involve β-cells encapsulated within a barrier to prevent them from immune attack and still allow nutrients and insulin to pass through.

Some researchers are also focussing on directly reprogramming other cell types within the body to form insulin-producing β-cells. This approach could eliminate the need for transplantation by regenerating insulin-producing cells within the individual.

Gene Therapies. Gene therapies for reinstituting basal insulinaemia and managing postprandial hyperglycaemia have been tested in animal models. Some gene therapy approaches, with longer follow-up periods in animal models, are preparing for "first-in-human" clinical trials. Genetically modified cell therapies are also being developed, with promising initial results.

Sustainable Research Priorities

Alongside healthcare 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 person-centred 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.

Anticipated Impact of Future Research

Research within the area of T1D has been rapidly evolving. Keeping T1D research priorities on the agenda promises a future where early detection, personalized therapies, and innovative technologies will transform individual 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 intervention and improved outcomes.

Moreover, the advent of wearable technology and AID 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 complications of T1D and cure strategies offers hope for a future, where the inclusion of real-world evidence and person-reported outcomes will significantly reduce the burden of the disease. Leveraging real-world evidence in T1D research is indispensable for advancing knowledge, enhancing treatment strategies, reducing healthcare disparities, and, ultimately, improving the quality of life of individuals affected by this chronic condition.

Stem cell research and β-cell protection strategies hold promise for achieving long-term remission or even a cure, transforming the lives of millions affected by T1D. In summary, research prioritization in T1D anticipates a future where personalized care, innovative technologies, and breakthrough therapies converge to improve personalized outcomes and emerge in a new era of hope and possibility for those living with the condition (Fig. 1).

Hyperinsulinism

Epidemiology, Societal Impact, and Research State of the Art

Congenital hyperinsulinism is a rare disease of insulin excess associated with severe and recurrent hypoglycaemia, which causes neuroglycopenia with lifelong neurodisability in about half of patients. Hyperinsulinism is a heterogeneous disease with an identified genetic aetiology in 50% of patients [176]. In many individuals, the cause and mechanism of illness remain unknown. Treatment options are limited, with diazoxide being the only medication approved by the US Food and Drug Administration, and second-line treatment with somatostatin analogues often complicated by side effects.

Patients with diffuse forms of hyperinsulinism, with involvement of the whole pancreas, are often unresponsive to standard medical therapies and require subtotal pancreatectomy [177]. Inevitably, they develop hyperglycaemia, although alternating with episodic hypoglycaemia, progressing to diabetes in teenage years [178]. In contrast, the treatment of the focal form of hyperinsulinism, 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 of cases [179].

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 hyperinsulinism face many challenges [180]. Therefore, research prioritization highlighting specific unmet needs is urgently required. This will advance the clinical management of hyperinsulinism, with improved diagnostics and effective treatment to improve the outcomes for patients and their families.

Future Research Priorities and Anticipated Impact

Diagnostics

Newborn Screening. A newborn screening tool is needed to identify neonates with hyperinsulinism as missed or delayed diagnosis leads to neurodevelopmental delay [180, 181]. Biomarker efficacy/validity studies, simulation models, and screening pilots will be needed. Research will comprise biomarker panel development, rapid screening for analytes, rapid gene panel screening, selected population pilot studies, and qualitative feedback.

Glucose as a Vital Sign. There is no clear definition of the depth, range, and extent of hypoglycaemia, so research is required to define hypoglycaemia and its severity in the context of hyperinsulinism and long-term patient outcomes. This will lead to better identification of hyperinsulinism for treatment purposes. Improved definition and thresholds for severity and duration of hypoglycaemia in glucose profiles will improve research outcomes and treatment goals [182]. This research will involve cohort studies investigating biomarker status correlating with the severity and duration of hypoglycaemia, natural history studies examining glucose profiles and neurodevelopmental outcomes, and CGM data set review. The methodology will include biomarker

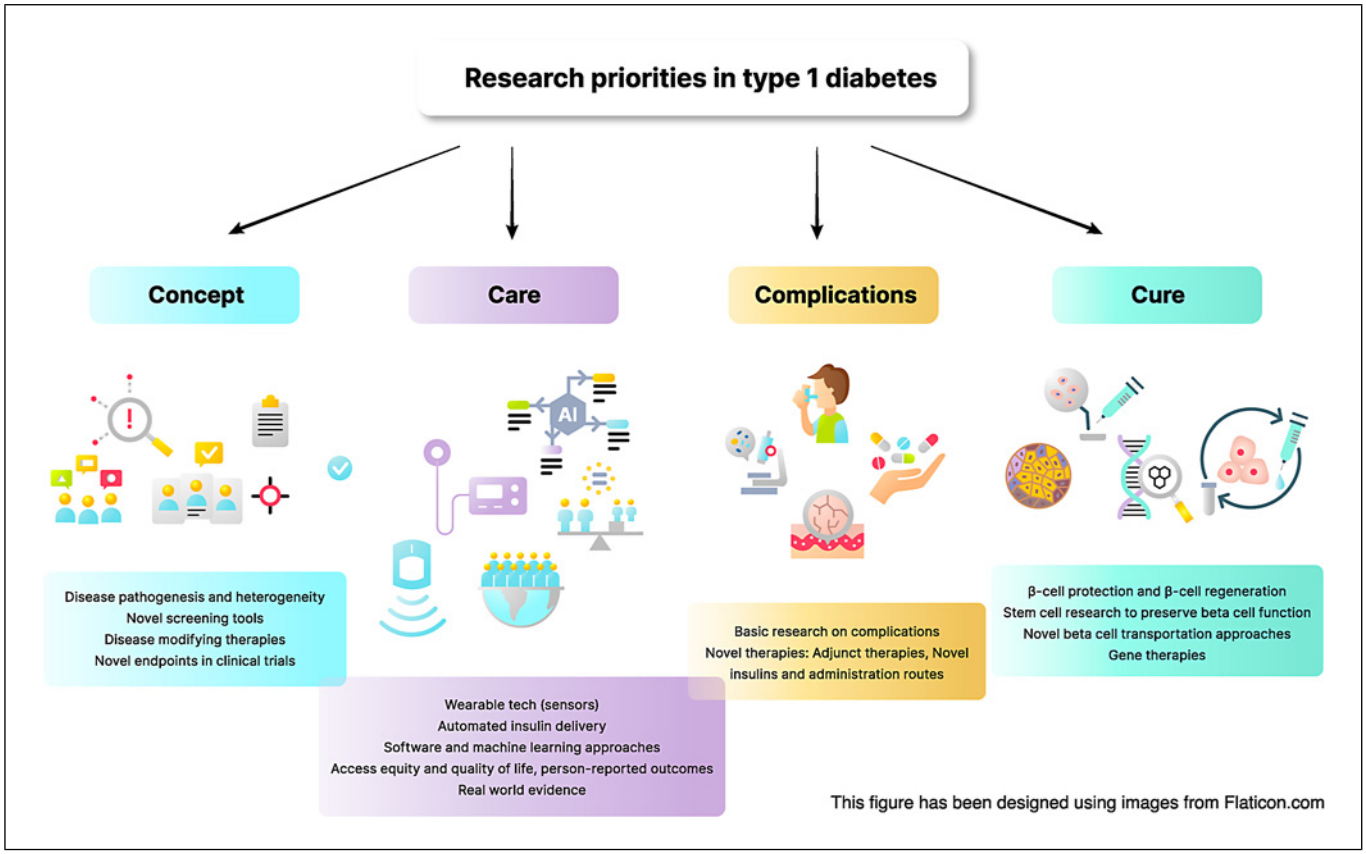

Fig. 1. Future research priorities in type 1 diabetes.

development, omics approaches correlating with biochemical phenotype, cross-sectional/longitudinal analysis of glycaemic information in patient-/clinician-reported databases, reviewing of CGM data, prospective CGM trials, and clinical trial outcome reviews.

Glucose Monitoring. Standard-of-care glucose monitoring, using infrequent blood glucose testing, results in missed episodes of hypoglycaemia. In addition, the research evidence for CGM as a replacement for blood glucose testing is incomplete. There is a need for improved glucose monitoring and interpretation to translate to clinical practice.

Profiling of CGM requires a robust evidence base and guidelines for effective use. The present generation of CGM sensors requires improvement, adaptation to hypoglycaemia, and demonstration of accuracy and efficacy [183, 184].

As well as the development of a hypoglycaemia-specific sensor, both CGM data set review and trials of CGM as a therapeutic management tool are needed, supported by qualitative studies involving families and patients. The work will include sensor and algorithm technology development, observational studies testing hypoglycaemia-specific CGM sensors/algorithms, analysis of CGM data sets using artificial intelligence, clinical trials of the efficacy of CGM in reducing hypoglycaemia, and qualitative studies with patient feedback.

Pancreatic Imaging. Current methods using radionuclide imaging are restricted to a few centres and limited by cost and set-up requirements, requiring expertise to produce high-quality consistent reports [185]. There is a need for the development of accurate and improved imaging of the pancreas, to identify focal lesions and exclude diffuse hyperinsulinism. Radiopharmaceutical development, clinical trials, and investigation of new imaging technologies will be supported by methodology related to novel radiochemistry, technology-assisted design, and innovative trial design minimizing radiation exposure.

Genetic Testing. Up to 50% of cases of persistent hyperinsulinism do not have an identified genetic aetiology. There is, therefore, a need to identify novel genetic

aetiologies, gene modifications and adaptations, and genetic mechanisms of hyperinsulinism, as well as to perform natural history phenotyping for genotypes. Genetic understanding is crucial to understanding the natural history, and for counselling and treatment choices. Understanding genetic association and causation may predict disease course and treatment response.

Hyperinsulinism gene panel screening is currently in a pilot phase. There is also potential for stem cell therapeutic strategies culminating in the development of an artificial pancreas. Further, the longitudinal phenotype of genetic hyperinsulinism is not well known and requires temporal evaluation [186, 187].

The necessary research work will comprise 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, and natural history studies. A range of methods will be employed, such as multiomics studies, single-cell RNA analysis, long-read sequencing, gene-replication studies in animal models, chaperone-protein development, bioresource/tissue-bank utilization studies, bioinformatics, universal genetic database development, and the use of reference natural history repositories.

Medical and Surgical Treatment

Pathogenesis of Neuroglycopenia. The impact of hypoglycaemia due to hyperinsulinism on the brain is not fully understood, so tools should be developed to improve knowledge in this area. It is important to understand pathways in hypoglycaemia, in order to prevent and treat neuronal injury. Neuroglycopenia has an adverse impact with lifelong neurodisability in patients with hyperinsulinism and requires improved understanding of its underlying mechanisms [188, 189].

Animal experiments will be needed to define hypoglycaemic neuronal injury, and gene expression studies will identify pathways of neuroglycopenia. Studies will include determining biomarkers of neuronal injury, imaging, cohort studies, natural history studies, and drug target identification to ameliorate neuroglycopenic injury. The research will involve animal brain simulation experiments, single-cell RNA profiling, neurophysiological studies, advanced imaging studies, investigation of natural history repositories, and artificial intelligence reviews of drug libraries to reverse neuronal injury.

Drug Design and Repurposing. There is a paucity of drugs to treat hyperinsulinism, and therefore, new drugs must be designed and existing therapies repurposed for use in the disease. Gene therapy constructs are needed to target specific mutations. Medical management must be improved for patients undergoing subtotal pancreatectomy and those with evolving diabetes.

Pipelines of drug development are long and expensive; hence, there is the 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 the teenage years [180].

Studies are needed for drug development targeting various insulin production/release pathways and of genotype-specific drug design, as well as clinical trials, artificial intelligence-based interrogation of drug libraries for repurposing, development of stem cell technologies, insulin infusion technologies, gene editing, development of vector constructs, real-world studies of newly developed and repurposed therapies, and bihormonal artificial pancreas algorithm development. The associated methodology will span physical chemistry, drug design and development, innovative study design and trials, stem cell studies, gene therapy development studies, real-world studies, trial design, and artificial pancreas trials.

Improved Surgical Techniques. Pancreatic surgical techniques are not refined and rely on surgical skill without assistance from technology. It is essential to develop surgical techniques that limit structural injury and minimize extent of surgery. Precision localization of the focal lesion and/or the boundaries of the lesion will retain pancreatic tissue and minimize long-term side effects. Integrating imaging, biomarkers and robotic techniques will aid surgeons in terms of safety and efficacy. Surgical training through virtual/augmented reality will ensure the retention of skill sets for future generations.

Conservation of surgical skills may be problematic with the decreasing emphasis on subtotal pancreatectomy. Tissue-sparing surgery is important to delay development of diabetes and minimize side effects. Imaging and robotic techniques could have real-time application during surgery, while virtual reality/augmented reality could reinforce skills training [180, 188].

The necessary studies will include improvement in imaging techniques, cohort studies assessing surgical choices, natural history studies, and studies of quality of life. They will employ imaging technology, robotic surgery instrumentation, acquisition of virtual reality-/augmented reality-assisted surgical skills, and a natural history review.

Real-World Studies, Clinical Trials, and Industry

There is significant patient need to reduce the burden of recurrent hypoglycaemia impacting on the brain. Novel therapies to treat and prevent hypoglycaemia are limited, and 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 [176, 180].

It is important to repurpose existing drug libraries to improve therapy choices in hyperinsulinism, and to design new medications with limited side effect profiles, and well as to develop small molecules for oral therapies. Preclinical studies, phase 1–3 studies, pharmacovigilance studies, choice of therapy outcome studies, observational cohort studies, and randomized blinded clinical trials are needed. These will incorporate cell and animal models, drug design and development, clinical trials, real-world studies, quality of life assessment, and qualitative patient feedback. Research in hyperinsulinism transition is expected to focus on changing illness behaviour in late childhood/early adult life, modulated by patient perceptions and feedback.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received.

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