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Advances in Gene Therapy Treatment for Obesity: A Mini-review

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Abstract

Obesity is a highly prevalent global pandemic that is rapidly growing. Recent advancements in gene therapy have opened new possibilities and targets for treating, especially monogenic forms of obesity. This mini-view identified novel preclinical developments in obesity genetic treatment over the past five years. Novel strategies targeting single or multiple genes or enzymes were identified as potential alternatives for existing treatment approaches. Although clinical trials for genetic obesity treatment are yet to emerge, novel preclinical treatment approaches based on genetic traits hold promise for addressing the obesity pandemic.

Introduction

Currently, the global pandemic of obesity is a complex multifactorial disease that affects more than 650 million adults worldwide and is rapidly growing (WHORO, 2022), making it one of the most significant contributors to ill health (Kopelman, 2000). Since 1975, the global incidence of obesity has tripled (The Lancet Gastroenterology Hepatology, 2021), which makes it a significant challenge to develop novel treatment strategies. Besides environmental and lifestyle factors, obesity is also influenced by a genetic predisposition (Loos & Yeo, 2022), which is the basis for developing novel gene therapeutic approaches.

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Besides syndromic obesity (e.g., Prader-Willi, Fragile X, or Cohen), non-syndromic obesity can be distinguished into a) Monogenic obesity, caused by specific pathogenic variants in single genes, and b) polygenic obesity, which is influenced by multiple genetic variants with small effect (Mahmoud et al., 2022). Although monogenic obesity is less common, an early onset, significant genetic effect, and a high penetrance are described (Loos & Yeo, 2022), making this a promising indication for a targeted gene therapeutic approach. However, combining different targets in a genetic therapy based on the patient's genetic profile in combination with other pharmacological and nonpharmacological treatments could also be a possible approach for polygenic obesity (Hinney et al., 2010). Due to the complex and ununderstood genetic pathogenetic pathway for obesity (Loos & Yeo, 2022), a monogenetic therapy is more rational for clinical translation. Most of the studies developing gene therapy for obesity treatment use a monogenic

targeting approach.

With the increasing clinical experiences of gene therapy-based treatments in recent years and the improvement and advances in genetic evaluation and analysis, many obesity-related genes have already been identified and preclinical evaluated. Obesity-related gene treatment targets involve Peroxisome Proliferator-Activated Receptor (PPAR) genes regulating adipocyte differentiation, low-density lipoprotein receptor genes, genes associated with circadian rhythm, glucocorticoid, and their receptor-associated genes participating in visceral fatty tissue expansion, and beta3-AR genes involved in lipolysis and thermogenesis (Gao & Liu, 2014). Moreover, targeting essential genes responsible for regulating energy balance, such as Growth Differentiation Factor 11 (Gdf11) or Fibroblast Growth Factor 21 (FGF21), as single or combination therapy by using viral vectors has yielded promising outcomes in preclinical studies, including effective weight loss, enhanced insulin sensitivity, and reduced fat mass (Jimenez et al., 2018; Lu et al., 2019). These findings suggest that gene therapy can potentially address the root causes of obesity by directly addressing the underlying genetic anomaly. In addition, gene therapy targeting obesity-associated diseases like type 2 diabetes mellitus or Non-Alcoholic Fatty Liver Disease (NAFLD) is in preclinical development, indicating the high potential of gene therapy (Banerjee et al., 2020; Weber et al., 2020).

This mini-view analyzes the safety and efficacy of current developments in genetic obesity treatment over the last five years, including current preclinical approaches.

Materials and Methods

This literature review used a pre-specified protocol and the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist (Page et al., 2021).

Search Strategy

As prescreening, a general search included mesh terms, subject heading terms, keywords, synonyms, alternate phrasing, and phrases related to those. Each author performed these individually to identify potential publications and relevant search terms for a systematic search. Two databases were selected for the search: (I) PubMed for preclinical and clinical data and (II) ClinicalTrials.gov register for finished ongoing or planned clinical trials. The investigation was restricted to articles or studies published in the last five years (cut-off date: 31st August 2023). The search was limited to in vivo animal and human studies with filters on the English language.

The systematic search strategy for (I) was performed using a predefined search term "((obesity[Mesh]) OR (anti-obesity drugs[mesh])) AND (gene therapy[mesh]). " The ClinicalTrials register (II) was used with the search terms "obesity" (condition) and "gene therapy" (intervention).

Study Criteria

Preclinical in vivo animal and human studies, clinical trials, prospective and retrospective studies, and case reports were eligible for inclusion if they included gene therapy as a single or combined interventional treatment against obesity. Therefore, initial criteria were extended for preclinical studies to provide a comprehensive review. Only studies published in peer-reviewed journals published in the English language were included. Following exclusion criteria were selected for the literature screening: Non-peer-reviewed articles, preprints, editorial commentaries, conference abstracts, reviews, and in vitro studies were excluded. CRIPSR/CAS-related gene editing therapies were excluded. Moreover, genetic treatment approaches for obesity-related diseases/indications were excluded.

Data Extraction

Different authors verified and performed the search procedure using the search terms for PubMed and the ClinicalTrials register. Identified studies and topics-related search results were cross-checked to fulfill the eligibility criteria defined. Bias was assessed using the SYRCLE's risk of bias tool for animal studies (Hooijmans et al., 2014). Moreover, relevant safety information was searched in the included publications. At least two authors double-checked each paper. Any disagreement in including a certain paper in the analysis was solved by discussion with a third author. Data extraction was supported by a web application-based automated reference and literature manager (Zotero online version 6.0.26, Corporation for Digital Scholarship) to support both abstract and full-text screening.

Results

Study Selection

Due to the absence of ongoing, planned, or finished clinical trials, this minireview includes preclinical data from animal experiments. The search revealed various in vivo studies, commentaries, reviews, and treatments of obesity-related diseases that were excluded according to the predefined eligibility criteria.

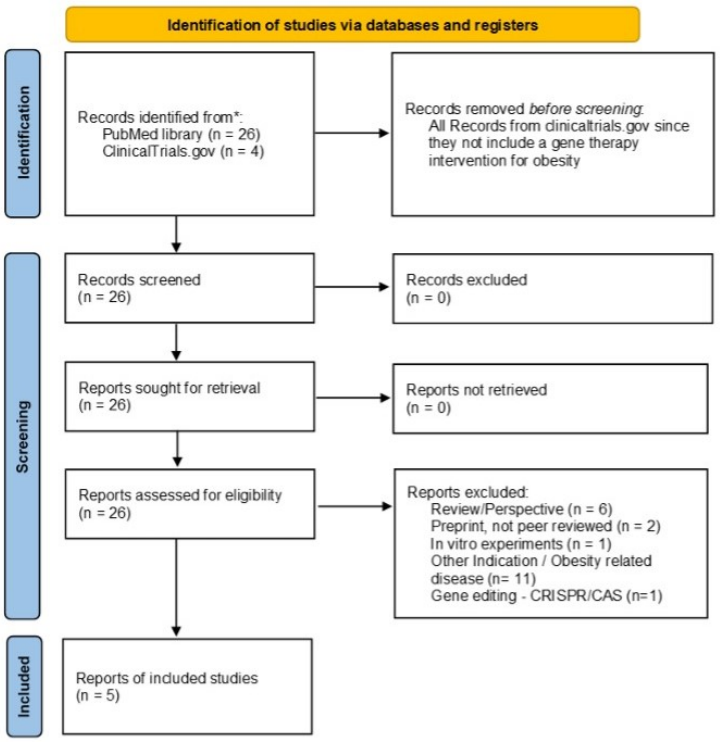

Figure 1: *PRISMA Flow diagram of the specified search term for gene therapy studies targeting obesity in the last five years (8).*

The resulting references encompass different gene therapy treatment approaches in different obesity animal models to study efficacy and safety. Collectively, these studies provide a comprehensive foundation for our review, enabling a comprehensive exploration of the field's current state and prospects. The search on the MEDLINE-Database identified 26 publications. Based on the selected inclusion and exclusion criteria, most of the studies needed to be excluded for different reasons (other indications (n=11), reviews/perspective (n=6), Preprints (n=2) only in vitro experiments (n=1), and CRISPR/CAS gene editing (n=1))—the study identification strategy in the PRISM flow diagram in Figure 1.

The search on the ClinicalTrials register showed the absence of ongoing, planned, or finished clinical trials in genetic obesity treatment in the last five years. The investigation resulted in 4 results that did not pass the eligibility criteria (no gene therapy treatment). Moreover, an extended search using related word variations led to more potential studies, but they still needed to pass the eligibility criteria. The investigation was limited to the last five years to identify the newest target strategies in the rapidly growing and developing gene therapy field and to extend existing reviews from the previous years (Gao & Liu, 2014; Hinney et al., 2022).

To strengthen the scope of this mini-review, CRISPR/CAS-related gene editing therapies were excluded from the search results. This was based on the complexity and variety of methods that need to be addressed in a separate review. Limited by our search terms, gene editing was not covered completely, which would limit the systematic search approach. Moreover, an overview of CRISPR/CAS-based treatments for obesity has already been covered in recently published reviews (Franco-Tormo et al., 2018; Jayachandran et al., 2023).

Study Characteristics

Based on the study selection, only preclinical in vivo experiments were included in the mini-review. The included studies showed various targets addressed in the treatment of obesity and encompassed a range of methodologies and approaches aimed at addressing obesity through gene therapy (Table 1). These investigations contribute valuable insights into the complex landscape of obesity treatment. The studies showed a high variety of different targets and treatment approaches that can be grouped into the following strategies: I) Single gene therapy treatment (single PRMD16 gene therapy phenotype in Skeletal Muscle (Chen et al., 2018); Bone Morphogenetic Protein 4 (BMP4) gene therapy (Hoffmann et al., 2020) and Gdf11 therapy (Lu et al., 2019)) II) combination therapy (BMP7/PRDM16/PGC-1a ectopic brown adipose tissue expression (Chen et al., 2018) and FGF21, αKlotho, and sTGFβR2 (Davidsohn et al., 2019) and III) enzyme engendering (Enoyl

Author	Title	Year	Animal	Treatment/Target	Outcome/Main findings	Safety
Chen, S. et al.	Ectopic BAT mUCP-1 overexpression in SKM by delivering a BMP7/PRDM16/PGC-1a gene cocktail or single PRMD16 using non-viral UTMD gene therapy	2018	Rats and mice	Gene therapy using ultrasound-targeted microbubble destruction (UTMD) ectopic brown adipose tissue (BAT) phenotype in skeletal muscle (SKM)	The weight loss obtained in the treated rats with the triple gene delivery, never recovered the levels observed in the controls in spite of food intake recovery.	No safety concerns or adverse outcomes are reported.
Davidsohn, N. et al.	A single combination gene therapy treats multiple age-related diseases.	2019	Mice	AAV8 modified vectors codifying 3 genes FGF21, αKlotho, and sTGFβR2, individually or combined	FGF21 alone or in combination was effective in weight loss, long-term weight maintenance, and insulin resistance.	No safety information is available. Improved surgical survival rates in treatment groups.
Hoffmann, J. M.et al.	BMP4 gene therapy enhances insulin sensitivity but not adipose tissue browning in obese mice	2020	Mice	Recombinant adenovirus-associated viral vectors of serotype 8 (AAV8) encoding a codon-optimized murine Bone morphogenetic protein 4 (Bmp4)	There was no effect on body weight, browning of white adipocyte tissue, or energy expenditure in mice. Insulin sensitivity and glucose tolerance had an improvement. Hepatic glucose production and gluconeogenic enzymes in the liver decreased.	No safety concerns or adverse outcomes are reported.
Lu, B. et al.	Gdf11 gene transfer prevents high fat diet-induced obesity and improves metabolic homeostasis in obese and STZ-induced diabetic mice.	2019	Mice	Gdf11 gene was transferred into the mice using hydrodynamic injection	Gdf11 gene transfer prevented HFD-induced obesity and metabolic disorders such as glycemia, insulin resistance, and fatty liver in mice. Moreover, Gdf11[8] gene transfer increased oxygen consumption, thermogenesis, and energy expenditure in mice.	No safety concerns or adverse outcomes are reported.
Mao, X. et al.	Enoyl coenzyme A hydratase 1 combats obesity and related metabolic disorders by promoting adipose tissue browning.	2020	Mice	Gene therapy using subcutaneous injection of AAV expressing murine ECH1 (mECH1) or a control virus expressing mCherry (mC) in bilateral inguinal white adipose tissue (iWAT) of mice	Overexpression of ECH1 led to a weight-sparing effect in mice, with less weight gain observed in the ECH1 overexpression group compared to the control group. In addition, the ECH1 overexpression group displayed improved glucose tolerance and insulin sensitivity.	No safety concerns or adverse outcomes are reported.

Table 1: *Summary of the identified studies.*

coenzyme A hydratase (Mao et al., 2020)).

Assessment of Risk of Bias and Safety in Individual Studies

The risk of bias in each selected study was assessed to ensure the quality and validity of the findings. Since the search strategy included animal experiments, SYRCLE's risk of bias tool for animal studies (Hooijmans et al., 2014) was utilized for risk assessments. The evaluation considered factors such as study design, sample size, blinding, randomization, and potential sources of bias. The results of the risk assessment are presented in Figure 2. The bias evaluation was limited by reporting information regarding the in vivo study design.

Moreover, all included studies do not report limitations due to severe toxic reactions (Table 1), independent of the different target approaches used in the studies. Importantly, all studies had a small sample size that is reasonable for the early stages of development. However, all included studies had appropriate control groups that increased the validity of the data.

Discussion

Obesity has become a global pandemic, posing a significant burden on public health. Traditional treatments such as lifestyle changes, medication, and bariatric surgery have limitations in long-term effectiveness and may lead to failures and side effects (4). Given the escalating obesity rates and associated health threats, there is an urgent need for innovative treatments.

Gene therapy holds promise in combating obesity, considering the pivotal role genetics plays in one's susceptibility to obesity (Speakman, 2004). Although the success of gene therapy in hematology and oncology has already reached clinical practice (e.g., CAR T cell therapy), to the best of our knowledge, no clinical trial for genetic obesity treatment has started yet. In the last decades, the Leptin pathway was identified as a promising treatment approach for obesity (Hinney et al., 2022). However, no clinical translation for genetic obesity treatment has been successful. Nevertheless, the results showed that new targets are the focus of preclinical research, confirming the need for novel treatments. Although most studies focused on monogenic obesity by targeting specific pathogenic variations, targeting multiple genes is also utilized to improve efficacy (Davidsohn et al., 2019).

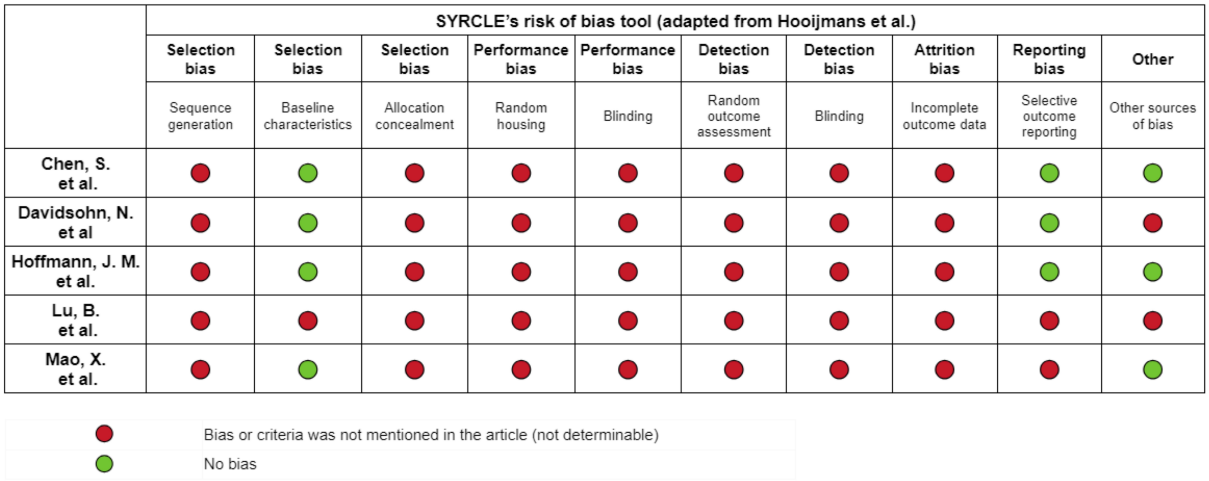

Figure 2: *Risk assessment for included studies based on the SYRCLE's risk of bias tool. The traffic-light scheme (green=no bias; red=bias observed or not possible to determine) represents the investigated bias of the studies.*

Several challenges must be addressed before gene therapy for obesity can be implemented clinically. A primary concern is the safe delivery of therapeutic gene therapies23 to specific tissues without triggering immune responses or unintended consequences, with a need for long-term safety and efficacy data. Moreover, the development and manufacturing of gene therapies are challenging, have high costs, and are time-consuming (Nishida et al., 2023; Srivastava et al., 2021). Although the reviewed studies used different delivery systems and targets, all identified studies reported no severe toxicities. Since safety concerns increase with the complexity of the treatment, targeting single genes may be more sufficient for a successful translation to the clinic. All the extracted studies can be considered as preliminary proof-of-concept approaches. Therefore, more research, including short-term and long-term toxicity studies, is needed to promote clinical translation.

This review covered novel developments in gene therapy. Nevertheless, limitations need to be considered. Several criteria restricted the search, e. g. language, which could have excluded some studies. The short time frame of 5 years had the disadvantage of only showing the current developments and limiting the number of reviewed publications. Limited reporting of details and no access to complete study protocols for animal trails in the reviewed publications hindered the exact evaluation of potential bias and safety in these studies. Moreover, the absence of clinical trials in humans and the inclusion of preclinical trials limit the relevance of clinical practice since translation in clinics is questionable.

Conclusion

This review identified novel preclinical genetic therapy strategies for obesity treatment. These approaches included single and multiple gene targeting approaches. Although a wide variety of potential targets has been identified, no clinical study is currently ongoing. Confirmatory studies are needed since the reviewed studies showed efficiency and no acute toxicities.

Abbreviations

PPAR: Peroxisome Proliferator-Activated Receptor
FGF21: Fibroblast Growth Factor 21
BMP4: Bone Morphogenetic Protein 4
Gdf11: Growth Differentiation Factor 11
NAFLD: Non-Alcoholic Fatty Liver Disease
CAR T cell therapy: Chimeric Antigen Receptor T cell therapy

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Conflicts of Interest

The authors declare no conflict of interest.

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