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Genotype-stratified treatment for monogenic insulin resistance: a systematic review

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Abstract

Background Monogenic insulin resistance (IR) includes lipodystrophy and disorders of insulin signalling. We sought to assess the effects of interventions in monogenic IR, stratified by genetic aetiology.

Methods Systematic review using PubMed, MEDLINE and Embase (1 January 1987 to 23 June 2021). Studies reporting individual-level effects of pharmacologic and/or surgical interventions in monogenic IR were eligible. Individual data were extracted and duplicates were removed. Outcomes were analysed for each gene and intervention, and in aggregate for partial, generalised and all lipodystrophy.

Results 10 non-randomised experimental studies, 8 case series, and 23 case reports meet inclusion criteria, all rated as having moderate or serious risk of bias. Metreleptin use is associated with the lowering of triglycerides and haemoglobin A1c (HbA1c) in all lipodystrophy ($n = 111$), partial ($n = 71$) and generalised lipodystrophy ($n = 41$), and in *LMNA*, *PPARG*, *AGPAT2* or *BSCL2* subgroups ($n = 72, 13, 21$ and 21 respectively). Body Mass Index (BMI) is lowered in partial and generalised lipodystrophy, and in *LMNA or BSCL2*, but not *PPARG* or *AGPAT2* subgroups. Thiazolidinediones are associated with improved HbA1c and triglycerides in all lipodystrophy ($n = 13$), improved HbA1c in *PPARG* ($n = 5$), and improved triglycerides in *LMNA* ($n = 7$). In *INSR*-related IR, rhIGF-1, alone or with IGFBP3, is associated with improved HbA1c ($n = 17$). The small size or absence of other genotype-treatment combinations preclude firm conclusions.

Conclusions The evidence guiding genotype-specific treatment of monogenic IR is of low to very low quality. Metreleptin and Thiazolidinediones appear to improve metabolic markers in lipodystrophy, and rhIGF-1 appears to lower HbA1c in INSR-related IR. For other interventions, there is insufficient evidence to assess efficacy and risks in aggregated lipodystrophy or genetic subgroups.

Plain language summary

The hormone insulin stimulates nutrient uptake from the bloodstream into tissues. In insulin resistance (IR), this action is blunted. Some rare gene alterations cause severe IR, diabetes that is difficult to control, and early complications. Many treatments have been suggested, but reliable evidence of their risks and benefits is sparse. We analysed all available reports describing treatment outcomes in severe IR. We found that the evidence is of low to very low quality overall. Injections of leptin, a hormone from fat tissue, or thiazolidinedione tablets that increase fat tissue both appear to improve diabetes control in people with reduced ability to make fat tissue. Injections of another treatment, insulin-like growth factor, appear to improve diabetes control in people with direct blockage of insulin action. There is a pressing need to improve evidence for treatment in these rare and severe conditions.

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Diabetes caused by single gene changes is highly heterogeneous in molecular aetiopathogenesis. It may be grouped into disorders featuring primary failure of insulin secretion, and disorders in which insulin resistance (IR), often severe, predates secondary failure of insulin secretion and diabetes. Monogenic IR is itself heterogeneous, encompassing primary lipodystrophy syndromes, primary disorders of insulin signalling, and a group of conditions in which severe IR is part of a more complex developmental syndrome[1].

Monogenic IR is rare but underdiagnosed. The commonest subgroup is formed by genetic lipodystrophy syndromes[2,3]. A recent analysis of a large clinical care cohort unselected for metabolic disease suggested a clinical prevalence of lipodystrophy of around 1 in 20,000, with a prevalence of plausible lipodystrophy-causing genetic variants of around 1 in 7000[4]. Monogenic IR is important to recognise, because affected patients are at risk not only of micro- and macrovascular complications of diabetes, but also of complications such as dyslipidemia, pancreatitis, and steatohepatitis, especially in lipodystrophy syndromes[5]. Non-metabolic complications specific to individual gene defects may also occur, including hypertrophic cardiomyopathy and other manifestations of soft tissue overgrowth[3]. Diabetes is also commonly the sentinel presentation of a multisystem disorder, and recognition of complex syndromes in a diabetes clinic may trigger definitive diagnostic testing.

The only therapy licensed specifically for monogenic IR is recombinant human methionyl leptin (metreleptin), with licensed indications encompassing a subset of patients with lipodystrophy and inadequate metabolic control. The current license in the USA is restricted to generalised lipodystrophy, but in Europe, it extends to some patients with partial lipodystrophy. A substantial proportion of the body of evidence considered in licensing addressed patients ascertained by the presence of clinical lipodystrophy, and the role of genetic stratification in the precision treatment of lipodystrophy has not been systematically addressed. Many other medications and other treatment options are also widely used in monogenic IR, although not licensed for that specific subgroup. Such use draws on the evidence base and treatment algorithms developed for type 2 diabetes. Several forms of monogenic IR have molecular and/or clinical attributes that suggest potential precision approaches to treatment.

We sought now to undertake a systematic review of the current evidence guiding the treatment of monogenic IR stratified by genetic aetiology, to assess evidence for differential responses to currently used therapies, to establish gaps in evidence, and to inform future studies. This systematic review is written on behalf of the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) *Precision Medicine in Diabetes Initiative* (PMDI) as part of a comprehensive evidence evaluation in support of the 2nd International Consensus Report on Precision Diabetes Medicine[6]. The PMDI was established in 2018 by the ADA in partnership with the EASD to address the burgeoning need for better diabetes prevention and care through precision medicine[7].

Our analyses show that metreleptin and thiazolidinediones appear to lower HbA1c, triglycerides, and body weight in patients with lipodystrophy of all genotypes, and rhIGF-1 appears to lower HbA1c in patients with *INSR*-related IR. For other interventions, there is insufficient evidence to assess efficacy and risks.

Methods
Inclusion criteria and search methodology. To assess the treatment of severe IR of known monogenic aetiology, with or without diabetes mellitus, including generalised and partial lipodystrophy and genetic disorders of the insulin receptor, we

developed, registered and followed a protocol for a systematic review (PROSPERO ID CRD42021265365; registered July 21, 2021)[8]. The study was reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Filtering and selection of studies for data extraction were recorded using the Covidence platform (https://www.covidence.org, Melbourne, Australia).

We searched PubMed, MEDLINE and Embase from 1987 (the year before the identification of the first monogenic aetiology of IR) to June 23, 2021 for potentially relevant human studies in English. We used broad search terms designed to capture the heterogeneity of monogenic IR and its treatments. We searched for studies addressing 1. Severe IR due to variant(s) in a single gene OR 2. Congenital generalised or familial partial lipodystrophy due to variant(s) in a single gene. We selected only studies that reported a treatment term, including but not limited to the mention of 1. Thiazolidinediones (TZD), 2. Metreleptin, 3. SGLT2 inhibitors, 4. GLP-1 analogues, 5. Bariatric surgery (all types), 6. Recombinant human IGF-1 or IGF-1/IGFBP3 composite, 7. U-500 insulin. No interventions were excluded in the primary search. In addition to the automated search, we hand searched reference lists of relevant review articles. Given the rarity of monogenic IR, no study types were excluded in the initial search. We ultimately considered experimental studies, case reports, and case series. The full search strategy is described in Supplementary Table 1.

Study selection for data extraction was performed in two phases, namely primary screening of title and abstract, then full text review of potentially eligible articles. Two authors independently evaluated eligibility, with discrepancies resolved by a third investigator. We excluded publications without original data, such as reviews, editorials, and comments, and those solely addressing severe IR or lipodystrophy of unknown or known non-monogenic aetiology, including HIV-related or other acquired lipodystrophies, or autoimmune insulin receptoropathy (Type B insulin resistance). Studies in which no clear categorical or numerical outcome of an intervention was reported, or in which interventions were administered for less than 28 days were also excluded.

Data extraction and outcome assessments. One author extracted data from each eligible study using data extraction sheets. Data from each study was verified by 3 authors to reach a consensus. Data were extracted from text, tables, or figures. Study investigators were contacted for pertinent unreported data or additional details where possible, most commonly genetic aetiology of insulin resistance in reported patients, and outcome data.

Data extracted for each study included first author, publication year, country, details of intervention, duration of follow-up, study design, and number of participants. Subject-level data were extracted for outcomes of interest, including sex, genetic cause of severe insulin resistance (gene name, mono- vs biallelic *INSR* pathogenic variant), phenotypic details of severe IR/lipodystrophic subtype (generalised vs partial lipodystrophy; associated syndromic features). Subject level outcome data were extracted prior to and after the longest-reported exposure to the intervention of interest for haemoglobin A1c (A1c), body mass index, serum triglyceride, ALT, or AST concentration, any index of liver size or lipid content, and total daily insulin dose. Potential adverse effects of interventions were recorded, including urinary tract infection, genital candidiasis, hypoglycemia, excessive weight loss, pancreatitis, soft tissue overgrowth, and tumour formation.

Risk of bias and certainty of evidence assessment. The quality of extracted case reports and case series was assessed using NIH

Study Quality Assessment Tools[9] by a single reviewer and verified by 2 additional reviewers. Grading of the overall evidence for specific research questions was undertaken as detailed in[10].

Statistics and reproducibility. Extracted data were managed using Covidence and analysed with SAS version 9.4. Pooled analysis was undertaken for all combinations of genotype and intervention for which sufficient numbers were reported, as well as for aggregated lipodystrophies, and generalized and partial subgroups of lipodystrophy. Generalized Estimating Equation models were used with time as a fixed factor and study as a random factor to examine treatment effects. Serum triglyceride concentrations were analyzed with and without log transformation. Data were summarized using estimated least-squared means with corresponding 95% confidence intervals.

Reporting summary. Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Identification of eligible studies. Initial searching identified 2933 studies, to which 117 were added from the bibliography reviews. 256 articles remained after the screening of titles and abstracts, and 44 after full text screening (Fig. 1).

Included studies addressed limited interventions and most had a high risk of bias. The 44 studies analysed and the assessment of their quality are summarised in Table 1 and detailed in Supplementary Data 1. Study quality was assessed as being fair in 15 cases and poor in 29 cases, including all case reports. This was primarily due to the high risk of bias, particularly related to the lack of a control group for all studies. Three of the 44 studies included in further analysis included only individuals already described in other reports and were discarded, leaving 41 studies for final analysis. These comprised 10 non-controlled experimental studies, 8 case series and 23 individual case reports (Table 1). No controlled trials were found. Individuals reported in the studies included 90 with partial lipodystrophy (72 due to *LMNA* mutation and 15 due to *PPARG* mutation), 42 with generalized lipodystrophy (21 *AGPAT2*, 21 *BSCL2*, 2 *LMNA*), and 19 with IR due to *INSR* mutation(s). Among the interventions described, only the responses to metreleptin (111 recipients), thiazolidinediones (13 recipients) and rhIGF-1 (alone or as a composite with IGFBP3) (17 recipients) were described in more than 5 cases (Table 1). This meant that for the large preponderance of possible genotype-treatment combinations no specific data were recovered (Supplementary Table 2). Full outcome data extracted are summarised in Supplementary Data 2, and subject-level data are shown in Supplementary Figures 1 through 8 with raw data provided in Supplementary Data 2.

Metreleptin treatment was associated with improved metabolic control in lipodystrophy. In our registered systematic review plan we posed several subquestions about treatment of monogenic IR subtypes that we felt were tractable. The first related to the risks and benefits (assessed by side effects, A1c, serum triglyceride concentration, body mass index (BMI), and indices of fatty liver) of metreleptin in patients with different monogenic subtypes of lipodystrophy. The response to metreleptin was
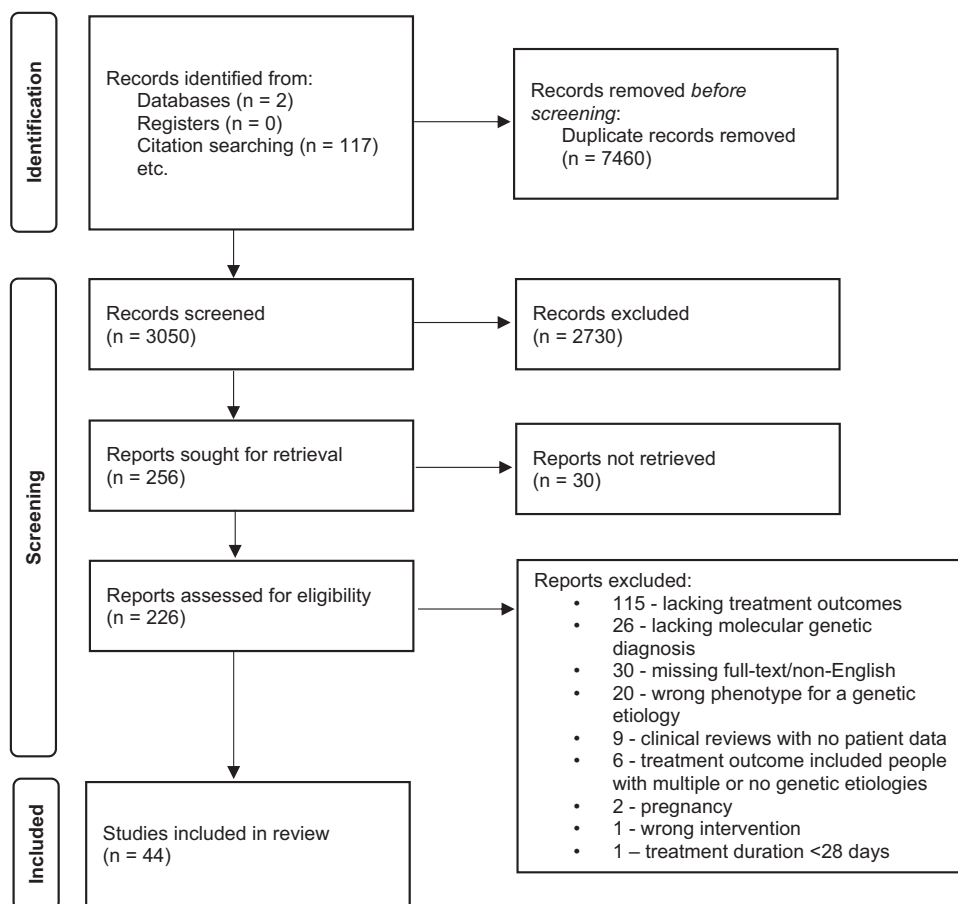

Fig. 1 PRISMA diagram. PRISMA flow diagram of publications evaluated based on the search strategy.

Table 1 Summary characteristics of included studies.

Study types	Number of studies
Case reports	23
Non-randomised experimental study	10
Case series	8
Study Quality*	**Number of studies**
Good	0
Fair	15
Poor	30
Phenotypes	**Number of participants**
Partial lipodystrophy	90
	(72 *LMNA*, 15 *PPARG*, 2 *PLIN1*, 1 *PIK3R1*)
Generalised lipodystrophy	56
	(21 *AGPAT2*, 21 *BSCL2*, 1 *PTRF*, 2 *LMNA*)
Insulin receptor	19 (7 Monoallelic, 12 Biallelic)
Intervention	**Number of participants#**
Metreleptin	111 (71/40/0)
rhIGF-1 or rhIGF-1/IGFBP3 composite	17 (0/0/17)
Thiazolidinedione	13 (12/1/0)
Metformin	5 (2/1/2)
Bariatric surgery	4 (4/0/0)
SGLT2i	2 (1/1/0)

*Based on NHLBI quality assessment tool; #Numbers in brackets are for partial lipodystrophy/ generalised lipodystrophy/ insulin receptor individuals respectively. *rhIGF-1* recombinant human insulin-like growth factor 1, *IGFBP3* insulin-like growth factor binding protein 3, *SGLT2i* sodium-glucose co-transporter-2 inhibitor

described in 111 people (71 with partial lipodystrophy, 40 with generalized lipodystrophy)[11–23]. Metreleptin was administered for 19 ± 20 months (median 12, range 1–108) and was associated with lowering of A1c in aggregated lipodystrophy, in generalized and partial subgroups, and in all genetic subgroups for whom sufficient patients were reported, namely those with *LMNA*, *PPARG*, *AGPAT2* and *BSCL2* mutations (0.5 to 1.5% least square mean reduction) (Level 3 evidence, Supplementary Data 3, Fig. 2). Metreleptin treatment was also associated with lowering of serum triglyceride concentration in aggregated lipodystrophy, in generalized and partial subgroups, and in those with *LMNA*, *PPARG*, *AGPAT2* and *BSCL2* mutations (92 to 1760 mg/dL least square mean reduction for analyses of untransformed data) (Level 3 evidence, Supplementary Data 3, Fig. 2). BMI was lower after treatment in aggregated lipodystrophy, in generalized and partial subgroups, and in those with *LMNA* or *BSCL2* mutations, but not *PPARG* or *AGPAT2* mutations (Level 3 evidence, Supplementary Data 3, Fig. 2). Liver outcomes reported were too heterogeneous to analyse in aggregate. Only a single adverse event, namely hypoglycemia, was reported.

Thiazolidinedione treatment showed variable efficacy in limited studies. We next addressed the evidence of the risks and benefits of thiazolidinediones (TZDs) in patients with lipodystrophy. We were specifically interested in any evidence of a greater or lesser response in partial lipodystrophy caused by *PPARG* variants than in other lipodystrophy subtypes, as TZDs are potent ligands for the product of the *PPARG* gene, the master regulator of adipocyte differentiation. The response to TZDs was described in only 13 people, however (12 FPLD, 1 CGL)[24–34]. TZDs were administered for 29 ± 28 months (median 24, range 2–96). TZD use was associated with improved A1c in aggregated lipodystrophy (least square mean reduction 2.2%) and in *PPARG*-related but not *LMNA*-related partial lipodystrophy (Level 4 evidence,

Supplementary Data 3, Fig. 3). Serum triglyceride concentration decreased in aggregated lipodystrophy and in those with *LMNA*-related but not *PPARG*-related partial lipodystrophy (Level 4 evidence, Supplementary Data 3, Fig. 3). No adverse events were reported.

rhIGF-1 treatment in INSR-related IR was associated with improvement in A1c. Our last specific question related to the risks (e.g. tumours, hypoglycemia, cardiac hypertrophy, other soft tissue overgrowth) and benefits (assessed by A1c) of recombinant human IGF-1 (rhIGF-1) or IGF-1/IGFBP3 composite in patients with pathogenic *INSR* variants. The response to rhIGF-1 was described in 17 people with pathogenic *INSR* variants for a mean of 45 ± 81 months (median 9, range 1–288)[35–46]. In *INSR*-related IR, we found that use of rhIGF-1, alone or as a composite with IGFBP3, was associated with improvement in A1c, and this was true also in subgroups with monoallelic and biallelic variants (1.5 to 2% least square mean reduction, Level 4 evidence, Supplementary Data 3, Fig. 4). One instance of increased soft tissue overgrowth and two episodes of hypoglycemia was reported.

Many questions about genotype-stratified treatment were not addressed. While many other interesting and clinically relevant questions arise about other potential genotype-specific responses to therapy in monogenic IR, the small size or absence of other genotype by treatment groups precluded the drawing of conclusions about risks and benefits, including for very widely used medications such as metformin[26,47–49], newer agents commonly used in type 2 diabetes including SGLT2 inhibitors[50,51] and GLP-1 agonists, and non pharmacologic interventions such as bariatric surgery[52–54].

Discussion

Thirty-five years since *INSR* mutations were identified in extreme IR[55,56], and 23 years since the first monogenic cause of lipodystrophy was reported[57], many different forms of monogenic IR are known[1–3,58]. These are associated with substantial early morbidity and mortality, ranging from death in infancy to accelerated complications of diabetes and fatty liver disease in adulthood, depending on the genetic subtype. Several opportunities for genotype-guided, targeted treatment are suggested by the causal genes, and so we set out to review the current evidence guiding the treatment of monogenic IR stratified by genetic aetiology. We found a paucity of high-quality evidence (all levels 3 to 4). No controlled trials of any intervention were identified, and there was substantial heterogeneity of study populations and intervention regimens, even for the same interventional agent.

The evidence which we did find, from a small number of uncontrolled experimental studies, augmented by case series and numerous case reports, suggests that metreleptin offers metabolic benefits across different lipodystrophy subtypes, in keeping with its licensing for use in some patients with lipodystrophy in both Europe and the USA. Notably, the evidence base considered by licensing authorities was larger than the one we present, including many studies of phenotypically ascertained lipodystrophy that included acquired or idiopathic disease. In contrast, we have addressed solely individuals with lipodystrophy caused by variation in a single gene. The limited data we identified do not clearly support differential effects among different monogenic lipodystrophy subgroups, but for many subtypes numbers reported are very small. Moreover, although responses appear comparable for partial and generalised lipodystrophy, this is highly likely to reflect selection bias in studies of partial lipodystrophy towards those with more severe metabolic complications and lower baseline serum leptin concentrations.
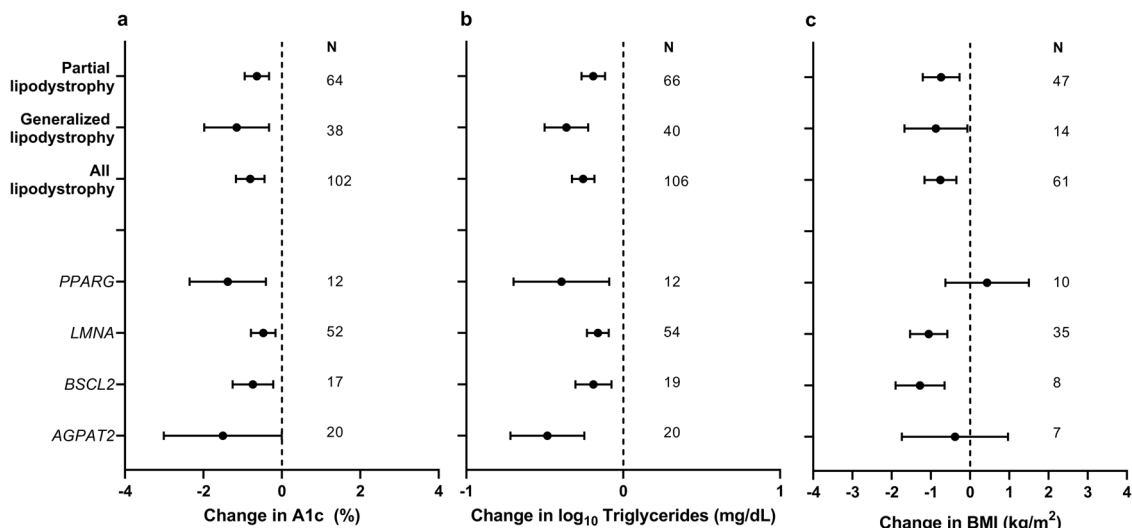
Fig. 2 Effects of metreleptin in monogenic forms of lipodystrophy. Least square mean change in (**a**) Hemoglobin A1c (A1c), (**b**) $\log_{10}$ serum triglyceride concentration and (**c**) Body Mass Index (BMI) in patients with partial lipodystrophy, generalized lipodystrophy, all forms of lipodystrophy, and subgroups with *PPARG, LMNA, BSCL2,* and *AGPAT2* mutations. Error bars represent 95% confidence intervals. $N = 64, 38, 102, 12, 52, 17,$ and 20 for change in A1c in partial lipodystrophy, generalized lipodystrophy, all lipodystrophy, *PPARG, LMNA, 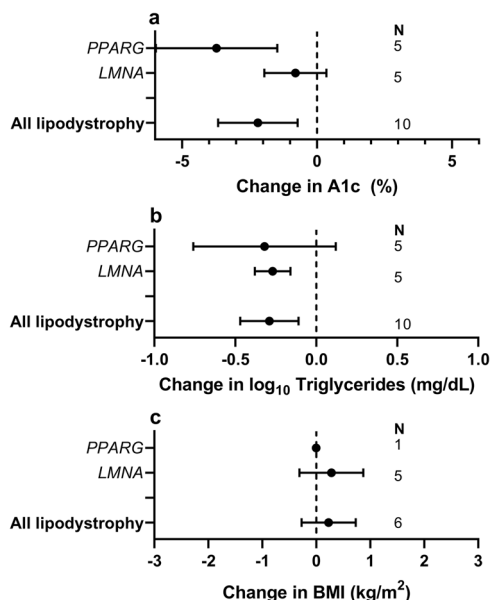BSCL2,* and *AGPAT2*-associated lipodystrophy, respectively. $N = 66, 40, 106, 12, 54, 19,$ and 20 for change in $\log_{10}$ triglycerides in partial lipodystrophy, generalized lipodystrophy, all lipodystrophy, *PPARG, LMNA, BSCL2,* and *AGPAT2*-associated lipodystrophy, respectively. $N = 47, 14, 61, 10, 35, 8,$ and 7 for change in BMI in partial lipodystrophy, generalized lipodystrophy, all lipodystrophy, *PPARG, LMNA, BSCL2,* and *AGPAT2*-associated lipodystrophy, respectively.

Fig. 3 Effects of thiazolidinediones in monogenic forms of lipodystrophy. Least square mean change in (**a**) Hemoglobin A1c (A1c), (**b**) $\log_{10}$ serum triglyceride concentration and (**c**) Body Mass Index (BMI) in patients with partial lipodystrophy, generalized lipodystrophy, all forms of lipodystrophy, and subgroups with *PPARG,* and *LMNA* mutations. Error bars represent 95% confidence intervals. $N = 5, 5,$ and 10 for change in A1c and change in $\log_{10}$ triglycerides in *PPARG, LMNA,* and all lipodystrophy, respectively. $N = 1, 5,$ and 6 for change in BMI in *PPARG, LMNA,* and all lipodystrophy, respectively.

A clear opportunity for precision diabetes therapy in monogenic IR is offered by the IR and lipodystrophy caused by mutations in *PPARG,* which encodes the target for thiazolidinediones (TZDs) such as pioglitazone[59,60]. PPARG is a nuclear receptor that serves as the master transcriptional driver of adipocyte differentiation, and so as soon as *PPARG* mutations were
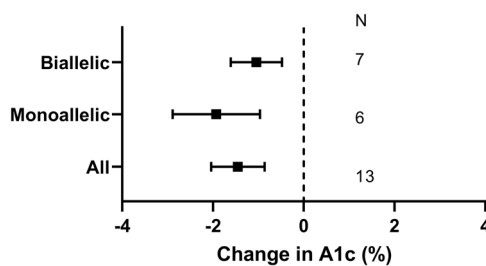

Fig. 4 Effects of recombinant human Insulin-like Growth Factor-1 (rhIGF) alone or in combination with Insulin-like Growth Factor Binding Protein-3 (IGFBP3) in patients with *INSR* mutations. Least square mean change in hemoglobin A1c (A1c), in all patients with *INSR* mutations, and in subgroups with biallelic and monoallelic mutations. Error bars represent 95% confidence intervals. $N = 7, 6,$ and 13 for biallelic, monoallelic, and all *INSR* mutations.

identified to cause severe IR, there was interest in the potential of TZDs as specific treatments. Although we found small scale evidence supporting greater A1c reduction with TZDs in *PPARG* vs. *LMNA*-related lipodystrophy, only 5 patients with *PPARG*-related lipodystrophy in whom TZD effects were clearly described were reported, and responses were inconsistent. Thus, it remains unclear whether people with IR due to *PPARG* variants are more or indeed less sensitive to TZDs than people with other forms of lipodystrophy. Loss-of-function *PPARG* mutations are the second commonest cause of familial partial lipodystrophy[2], and the function of coding missense variants in *PPARG* has been assayed systematically to accelerate genetic diagnosis[61], so the opportunity to test genotype-related therapy in *PPARG*-related IR seems particularly tractable in future.

Other obvious questions about the targeted treatment of monogenic, lipodystrophic IR are not addressed by current evidence. Important examples relate to the risks and benefits of treatments used in type 2 diabetes such as GLP-1 agonists and SGLT2 inhibitors. It is rational to suppose that these medications, which decrease weight as well as improve glycaemia in those with

raised BMI and diabetes, may also be efficacious in lipodystrophy even where BMI is normal or only slightly raised. This is because in both situations adipose storage capacity is exceeded, leading to fat failure. It is the offloading of overloaded adipose tissue, rather than the baseline BMI/adipose mass, which underlies the efficacy of therapy. However, GLP-1 agonists are contraindicated in those with prior pancreatitis, while SGLT2 inhibitor use can be complicated by diabetic ketoacidosis. In untreated lipodystrophy pancreatitis is common, yet this is due to hypertriglyceridaemia, which is likely to be improved by GLP-1 agonist use, while excessive supply of free fatty acids to the liver may promote ketogenesis. Thus, assessment of both classes of drugs in lipodystrophy and its genetic subgroups will be important to quantify risks and benefits, which may be distinct from those in obesity-related diabetes.

A further question we prespecified related to the use of rhIGF1 in people with severe IR due to *INSR* mutations. This use of rhIGF-1 was first described in recessive *INSR* defects in the early 1990s[44], and several studies of rhIGF-1 therapy of duration less than 28 days in people with *INSR* mutations have provided proof of concept for acute metabolic benefits (summarized in[38]). This use of rhIGF-1 is based on the rationale that IGF-1 activates a receptor and signalling pathway very closely similar to those activated by insulin. Based on case reports, case series and narrative reviews, rhIGF-1 is now commonly used in neonates with extreme IR due to biallelic *INSR* mutations, although, unlike metreleptin in lipodystrophy, this use is still unlicensed. Our review of published data, which was limited to durations of intervention greater than 28 days, is consistent with glycaemic benefits of rhIGF-1, alone or in composite form with its binding protein IGFBP3, in people with *INSR* mutations. Nevertheless, such studies are challenging to interpret and are potentially fraught with bias of different types, particularly publication bias favouring positive outcomes. Responses to rhIGF1 are also challenging to determine in uncontrolled studies as small differences in the residual function of mutated receptors can have substantial effects on the severity and natural history of the resulting IR, yet relatively few *INSR* mutations have been studied functionally. This underlines the narrow nature of, and substantial residual uncertainty in, the evidence base for the use of rhIGF-1 in monogenic IR.

There are several reasons why important questions about the precision treatment of monogenic IR have not been settled. Although severe autosomal recessive IR is usually detected in infancy, commoner dominant forms of monogenic IR are often diagnosed relatively late, often only after years of management based on presumptive diagnoses of type 2 or sometimes type 1 diabetes. Initial management as type 2 diabetes means that by the time a clinical and then genetic diagnosis is made, most patents have been treated with agents such as metformin, and increasingly SGLT2 inhibitors or GLP-1 agonists, outside trial settings. It is not clear that harm is caused by such use of drugs with well-established safety profiles and efficacy in type 2 diabetes, but the lack of systematic data gathering precludes the identification of specific drug-genotype interactions. Moreover, because attempts to gather evidence for monogenic IR treatment have tended to focus on high-cost adjunctive therapies such as metreleptin, the evidence base for their use is better developed, although controlled trials are lacking. Licensing of high-cost treatments such as metreleptin in lipodystrophy, while effects of many more commonly used, cheaper drugs with well-established safety profiles lack formal testing in monogenic IR is potentially problematic, skewing incentives and guidelines towards expensive therapy before optimal treatment algorithms have been established.

Other challenges in conducting trials in monogenic IR arise from the exquisite sensitivity of IR to exacerbating factors such as puberty, diet, and energy balance. This creates a signal to noise problem particularly problematic in uncontrolled studies, in which non-pharmacological components of interventions such as increased support for behavioural change may confound attribution of beneficial outcomes to pharmacological agents tested.

The key question now is how the evidence base for managing monogenic severe IR can be improved in the face of constraints in studying rare, clinically heterogeneous, and geographically dispersed patients who are often diagnosed late with a condition that is exquisitely environmentally sensitive. Growing interest in and development of methodologies for clinical trials in rare disease[62], including Bayesian methodologies[63,64], and hybrid single- and multi-site designs[65] offer hope for future filling of evidence gaps. One important and pragmatic opportunity arises from the development of large regional, national and international networks and registries for lipodystrophy (e.g. the Europe-based ECLip registry[66]), allied to emergence of randomised registry-based trial (RRT) methodology[67,68]. RRTs have attracted increasing interest in several disease areas and are particularly suitable for evaluation of agents with well-established safety profiles. When a simple randomisation tool is deployed in the context of a registry, RRTs can offer rapid, cost-effective recruitment and high external validity (i.e. relevance to real world practice). In monogenic IR this would permit questions to be addressed about optimal usage of different common medications in different genetic subgroups, including the order of introduction of therapies, and their optimal combinations. The quality of such studies will critically rely on good registry design and quality and completeness of data capture[67,68].

In summary, severe monogenic IR syndromes are clinically and genetically heterogeneous, with high early morbidity and mortality. However, despite opportunities for targeted therapy of some monogenic subgroups based on the nature of the causal gene alteration, the evidence for genotype-stratified therapy is weak. This is in part because of the rarity and frequent late diagnosis of monogenic IR, but also because therapeutic research to date has focused largely on phenotypically ascertained cross cutting diagnoses such as lipodystrophy. We suggest that approaches such as RRTs hold the best hope to answer some of the persisting major questions about precision treatment in monogenic IR.

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Author contributions

R.K.S., R.J.B., and K.A.P. researched data, wrote the manuscript, and reviewed and approved the final manuscript. S.A. conducted statistical analyses and reviewed and approved the final manuscript. Members of the ADA/EASD PMDI Consortium provided feedback on methodology and reporting guidelines.

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Additional information

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