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Telomir-Zn restores glucose homeostasis and reduces insulin resistance in a diet-induced zebrafish model of type 2 diabetes

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycemia driven by insulin resistance and metabolic dysregulation. Therapeutic strategies that restore insulin sensitivity remain a major unmet clinical need. In this study, we evaluated the metabolic effects of Telomir-Zn and its non-ion-chelated ligand, Telomir-1, in a diet-induced zebrafish model of non-insulin-dependent diabetes mellitus (NIDDM). Adult zebrafish were fed a high-calorie diet for six weeks to induce obesity-associated metabolic dysfunction characterized by insulin resistance and hyperglycemia. Fish were then treated with Telomir-Zn or Telomir-1 at three dose levels (0.5, 1.5, and 5 μg) for 14 days. Metabolic outcomes included fasting blood glucose, oral glucose tolerance testing (OGTT), fasting insulin concentrations, and insulin resistance assessed using the homeostatic model assessment of insulin resistance (HOMA-IR). Telomir-Zn produced a significant and dose-dependent reduction in fasting glucose levels and improved glucose clearance during OGTT. Treatment also reduced fasting insulin levels and significantly improved insulin sensitivity. Insulin resistance was markedly reduced, with HOMA-IR values decreasing from approximately 10 to 12 in diabetic fish to approximately 3 in treated groups. These findings demonstrate that Telomir-Zn restores key metabolic parameters associated with insulin resistance in a zebrafish model of T2DM and support further investigation of metal-modulating small molecules as a potential therapeutic strategy for metabolic disease.

1. Introduction

T2DM is a multifactorial metabolic disorder characterized by chronic hyperglycemia resulting from impaired insulin action and progressive β-cell dysfunction. The global prevalence of T2DM has increased dramatically over the past several decades and is closely associated with obesity, sedentary lifestyles, and metabolic syndrome [1,2]. Insulin resistance in peripheral tissues, particularly skeletal muscle, liver, and adipose tissue, represents a central pathogenic mechanism driving the progression of the disease [3–5].

Zebrafish (*Danio rerio*) have emerged as a powerful vertebrate model for investigating metabolic disorders, including obesity and diabetes. Key endocrine pathways regulating glucose homeostasis are highly conserved between zebrafish and mammals, including insulin signaling, glucose transport, and pancreatic endocrine regulation [6–7]. Diet-induced metabolic dysfunction in zebrafish reproduces essential features of human T2DM, including hyperglycemia, hyperinsulinemia, impaired glucose tolerance, and insulin resistance [8,9]. Consequently, zebrafish models represent a robust platform for studying metabolic disease mechanisms and screening therapeutic candidates that modulate glucose homeostasis [10,11].

In addition to classical metabolic pathways, growing evidence

Abbreviations: AAALAC, Association for Assessment and Accreditation of Laboratory Animal Care; ANOVA, Analysis of Variance; AUC, Area Under the Curve; CPCSEA, Committee for the Purpose of Control and Supervision of Experiments on Animals; ELISA, Enzyme-Linked Immunosorbent Assay; FG, Fasting Glucose; GLP-1, Glucagon-Like Peptide-1; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IAEC, Institutional Animal Ethics Committee; KDM, Histone lysine demethylase; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, Oral Glucose Tolerance Test; OD, Optical Density; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; PTP1B, Protein tyrosine phosphatase 1B; ROS, Reactive Oxygen Species; SEM, Standard Error of the Mean; SGLT2, Sodium-Glucose Cotransporter-2; T2DM, Type 2 diabetes mellitus; TELOMIR-1, 2,4,6-tri(3,4-dihydro-2H-pyrrol-2-yl) pyridine; Telomir-Zn, 2,4,6-tris(3,4-dihydro-2H-pyrrol-2-yl) pyridine zinc chloride complex; WT, wild-type; Zn, Zinc.

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suggests that dysregulation of transition metal homeostasis may contribute significantly to the pathogenesis of metabolic disease. Iron overload has been strongly associated with the development of insulin resistance and T2DM in both epidemiological and experimental studies. Elevated body iron stores, reflected by increased serum ferritin levels, correlate with a higher risk of T2DM and metabolic syndrome [12–14]. Mechanistically, excess labile iron can catalyze Fenton reactions that generate reactive oxygen species (ROS), leading to oxidative stress, mitochondrial dysfunction, and impaired insulin signaling pathways. Iron-induced oxidative stress can disrupt insulin receptor signaling and glucose transport through several mechanisms, including activation of inflammatory pathways and impairment of mitochondrial metabolism. Iron accumulation in pancreatic β-cells may also contribute to β-cell dysfunction and impaired insulin secretion, further exacerbating metabolic dysregulation [12,15,16]. Clinical observations from disorders characterized by iron overload, such as hereditary hemochromatosis, further support a causal relationship between excess iron and the development of diabetes [16].

Conversely, zinc plays a protective and regulatory role in glucose metabolism. Zinc is essential for insulin crystallization, storage, and secretion in pancreatic β-cells and contributes to multiple intracellular signaling pathways involved in glucose homeostasis. Zinc ions also possess antioxidant properties and may counteract the oxidative stress generated by excess redox-active metals such as iron and copper [17, 18]. Accordingly, modulation of intracellular metal balance has emerged as a potentially novel therapeutic strategy for metabolic disease.

The compound investigated in the present study, Telomir-Zn (2,4,6-tris(3,4-dihydro-2H-pyrrol-2-yl) pyridine zinc chloride complex), combines a small-molecule ligand capable of interacting with transition metals with a coordinated zinc ion. Telomir-Zn combines a metal-interacting ligand with coordinated zinc. This design is intended to influence cellular metal homeostasis and redox balance [19,20]. In previous studies, Telomir-Zn was shown to interact with labile intracellular metal pools, having highest affinity to copper and iron and less so to Zinc. Telomir-Zn inhibited multiple Fe^{2+}-dependent Jumonji C histone demethylases (KDM2, KDM5, and KDM6 families) and was shown to reduce reactive oxygen species and reduce metal-ion dependent calcium release in several cell types [19,20].

In this study, we evaluated the metabolic effects of Telomir-Zn and its ligand Telomir-1 in a diet-induced zebrafish model of non-insulin-dependent diabetes mellitus (NIDDM). Key metabolic parameters including fasting blood glucose, oral glucose tolerance, serum insulin levels, and HOMA-IR were assessed to determine whether these compounds can restore glucose homeostasis and improve insulin sensitivity in a model of diet-induced metabolic dysfunction. These findings position Telomir-Zn as a candidate therapeutic approach targeting upstream metabolic dysregulation through modulation of metal homeostasis and redox balance.

2. Materials and methods

Telomir-Zn (Fig. 1) is a zinc-complexed small molecule consisting of 2,4,6-tris(3,4-dihydro-2H-pyrrol-2-yl)pyridine coordinated with $ZnCl_2$. The compound was synthesized by Recipharm (Israel) and supplied at a purity of 95%.

Wild-type adult zebrafish (Danio rerio, AB strain, 4–6 months old, mixed sex) were maintained under standard laboratory conditions in accordance with AAALAC and CPCSEA guidelines. Fish were housed in 10-L recirculating aquaria (maximum density 5 fish/L) with a 14:10 h light–dark cycle at 27 ± 1°C. To induce metabolic dysfunction, zebrafish were fed a high-calorie diet for six weeks consisting of approximately 47.5% protein, 15.5% fat, 35% carbohydrates, and 2% fiber. Adult fish selected for the study were screened purposively, ensuring the inclusion of healthy individuals with no visible signs of infection, an average body weight of 0.8 ± 0.2 g, and an age of 1.5 years.

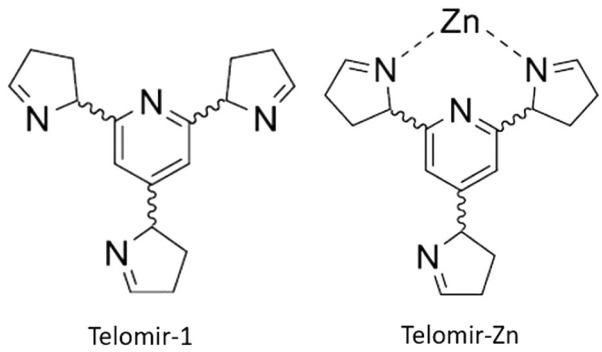

Fig. 1. Structure of Telomir-1 and Telomir-Zn, with the proposed chelation of zinc ion.

Fish were allocated into eight experimental groups: vehicle control, NIDDM model, Telomir-Zn (0.5, 1.5, and 5 μg), and Telomir-1 (0.5, 1.5, and 5 μg). Compounds were administered orally via compound-infused feed pellets for 14 consecutive days. The selected dose range (0.5, 1.5, and 5 μg) was based on preliminary tolerability and exploratory efficacy studies in zebrafish, as well as alignment with previously reported dosing strategies for small-molecule metabolic modulators in this model system. The selected range was intended to capture sub-therapeutic, intermediate, and near-maximal pharmacological effects while maintaining tolerability.

2.1. Formulated feeds – study compound infused feed preparation and feeding cycle

To prepare the infused oral feeds, the daily required dose of the test compound was mixed with 4 mg of standard commercial fish feed. The mixture was homogenized thoroughly, and the resulting feed was extruded into pellets, each standardized to a dry weight of 4 mg per pellet. These pellets were prepared for all study groups and stored at −20°C until use.

The study groups were fed on a 6-hour feeding cycle. During the light phase and dark phase, fish received compound-infused feed pellets in the morning and high-calorie pellets (15 mg/pellet/fish/day) in the evening. During each dosing session, fish were individually isolated from the study tanks to ensure accurate dosing and consumption of the compound-infused feed.

Control (vehicle) groups were fed standard commercial fish feed under identical conditions to those of the treatment groups, ensuring consistency in handling and feeding protocols.

2.2. Fasting blood glucose

Fasting blood glucose levels were measured using a glucometer. Fish were sedated in ice-cold water (14–16°C) for approximately 30 s, after which the fish were placed laterally on a dissection tray with minimal water.

Approximately 5 μL of blood was carefully extracted along the body axis, posterior to the cloaca, targeting the dorsal aorta region using a precision glass capillary needle. The collected blood was promptly transferred onto a glucometer strip to ensure immediate analysis, and glucose readings were recorded for further evaluation.

2.3. Blood glucose homeostasis by oral glucose tolerance test (OGTT)

Blood glucose homeostasis was assessed using an oral glucose tolerance test (OGTT), where the time required for fish to restore baseline blood glucose levels served as a measure of glucose homeostasis.

Glucose was dissolved in water and administered via oral gavage at a

dose of 1.25 mg per gram of body weight. Blood glucose levels were monitored at 0.5, 1, 1.5, 2, and 2.5 h following glucose administration using a glucometer to evaluate the kinetics of glucose clearance.

2.4. Fasting serum insulin

Fasting serum insulin concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Invitrogen; Cat# KAQ1251) according to the manufacturer's instructions.

The sandwich ELISA is designed to measure the amount of the target bound between a matched antibody pair. A target-specific antibody is precoated in the wells of the supplied microplate. Samples, standards, or controls are then added to the wells and bind to the immobilized capture antibody.

The sandwich complex is formed by the addition of a second detector antibody, after which a substrate solution is added that reacts with the enzyme-antibody complex to produce a measurable signal. The intensity of this signal is directly proportional to the concentration of the target present in the original specimen.

A standard curve was generated prior to sample analysis. Optical density (OD) readouts were measured spectrophotometrically at 450 nm ± 2 nm. The OD values were used to determine serum insulin concentrations by interpolation from the standard calibration curve.

2.5. Sample pooling and analysis

Insulin levels were assessed using fasting serum samples. For each time point, samples were pooled from six fish, with two independent pools per group. The average OD values from the replicate pools were used for the final analysis to ensure accuracy and reproducibility of the measurements.

2.6. HOMA-IR

The homeostatic model assessment of insulin resistance (HOMA-IR) was used to estimate insulin resistance in the fasting state.

HOMA-IR values were calculated using fasting insulin (IF) and fasting glucose (GF) according to the following equation:

$$\text{HOMA-IR} = (\text{Fasting serum insulin} \times \text{fasting blood glucose})/12$$

The denominator of 12 represents a normalization factor derived from the product of normal fasting plasma insulin (3 μIU/mL) and normal fasting plasma glucose (4 mmol/L), obtained from the vehicle control group.

A HOMA-IR value < 2 was considered indicative of normal insulin sensitivity.

2.7. Data processing

Statistical analysis of the data was performed using GraphPad Prism version 10 and results were expressed as mean ± SEM. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test to assess pairwise differences between all groups, including comparisons between treatment groups. Data are presented as mean ± SEM. This allowed direct evaluation of differences between vehicle control, NIDDM model, and each dose level of Telomir-Zn and Telomir-1. Significant differences were defined at $p \leq 0.05$ (*), $p \leq 0.01$ (), $p \leq 0.001$ (*), and $p \leq 0.0001$ (). Values labeled ns were considered not statistically significant.

3. Results

Diet-induced diabetic zebrafish exhibited markedly elevated fasting glucose levels compared with wild-type controls.

Among the treated groups, both Telomir-Zn and Telomir-1 demonstrated dose-dependent efficacy in reducing fasting blood glucose levels, with near-baseline glucose levels observed at doses of 1.5 μg and 5 μg on both day 7 and day 14 ($p \leq 0.0001$) (Fig. 2).

Glucose tolerance testing revealed significantly elevated OGTT profiles and increased area under the curve (AUC) values in diabetic fish, indicative of impaired glucose clearance and suggesting the presence of insulin resistance or reduced insulin sensitivity. These findings confirm the metabolic dysfunction characteristic of the NIDDM model.

A dose-dependent improvement in OGTT profiles was observed in the Telomir-Zn treated groups, whereas the effect of Telomir-1 was more modest on this parameter (Fig. 3).

The AUC represents the cumulative glucose exposure over time following glucose administration and provides a measure of the efficiency with which glucose is cleared from the bloodstream.

Notably, a significant reduction in AUC was observed in the Telomir-Zn treated group at the 1.5 μg and 5 μg doses, demonstrating a dose-dependent therapeutic effect that mitigates impaired glucose metabolism. A smaller, although significant effect, was observed at all doses of Telomir-1 (Fig. 4).

This reduction in AUC, observed at both day 7 and day 14, underscores the potential therapeutic effect of Telomir-Zn in restoring insulin sensitivity and improving glucose clearance in the diabetic model.

Serum insulin levels in the study groups were measured using an ELISA assay, and the data are presented as mean ± standard deviation. A five-fold elevation in serum insulin levels was observed in the NIDDM model, consistent with the presence of insulin resistance.

Treatment with Telomir-Zn resulted in a dose-dependent reduction in fasting serum insulin levels, suggesting improved insulin sensitivity and mitigation of hyperinsulinemia.

Similarly, treatment with Telomir-1 demonstrated a reduction in fasting serum insulin levels at both day 7 and day 14; however, this reduction did not display clear dose dependency, indicating a less predictable response compared with Telomir-Zn.

HOMA-IR values serve as a robust indicator of insulin sensitivity, reflecting the efficiency of glucose uptake by cells and the overall functionality of insulin in maintaining glucose homeostasis. Elevated HOMA-IR values are indicative of insulin resistance, a hallmark feature of the NIDDM model.

In the present study, a significant elevation in HOMA-IR values was observed in the untreated NIDDM group, confirming the presence of pronounced insulin resistance and impaired glucose regulation (Fig. 5).

Upon therapeutic intervention with Telomir-Zn and Telomir-1, a notable reduction in HOMA-IR values was observed, demonstrating their efficacy in ameliorating insulin resistance.

The reduction in HOMA-IR was particularly pronounced in the Telomir-Zn treated groups, with higher doses showing greater improvements in insulin sensitivity. This effect was consistently observed across both day 7 and day 14, indicating sustained metabolic improvement over the treatment period (Fig. 5).

These findings suggest that both Telomir-Zn and Telomir-1 exert beneficial effects on insulin resistance, with Telomir-Zn demonstrating a more consistent and dose-dependent response.

The observed improvements in HOMA-IR values further support the potential of these treatments to correct metabolic disturbances associated with NIDDM and improve glucose–insulin homeostasis.

4. Discussion

The present study demonstrates that Telomir-Zn significantly improves multiple metabolic parameters in a diet-induced zebrafish model of NIDDM. Treatment with Telomir-Zn resulted in a dose-dependent reduction in fasting blood glucose levels, improved glucose clearance during OGTT, and a marked reduction in insulin resistance as reflected by HOMA-IR values. These findings indicate that Telomir-Zn effectively restores glucose homeostasis in this diabetic zebrafish model.

The metabolic phenotype observed in the untreated NIDDM group

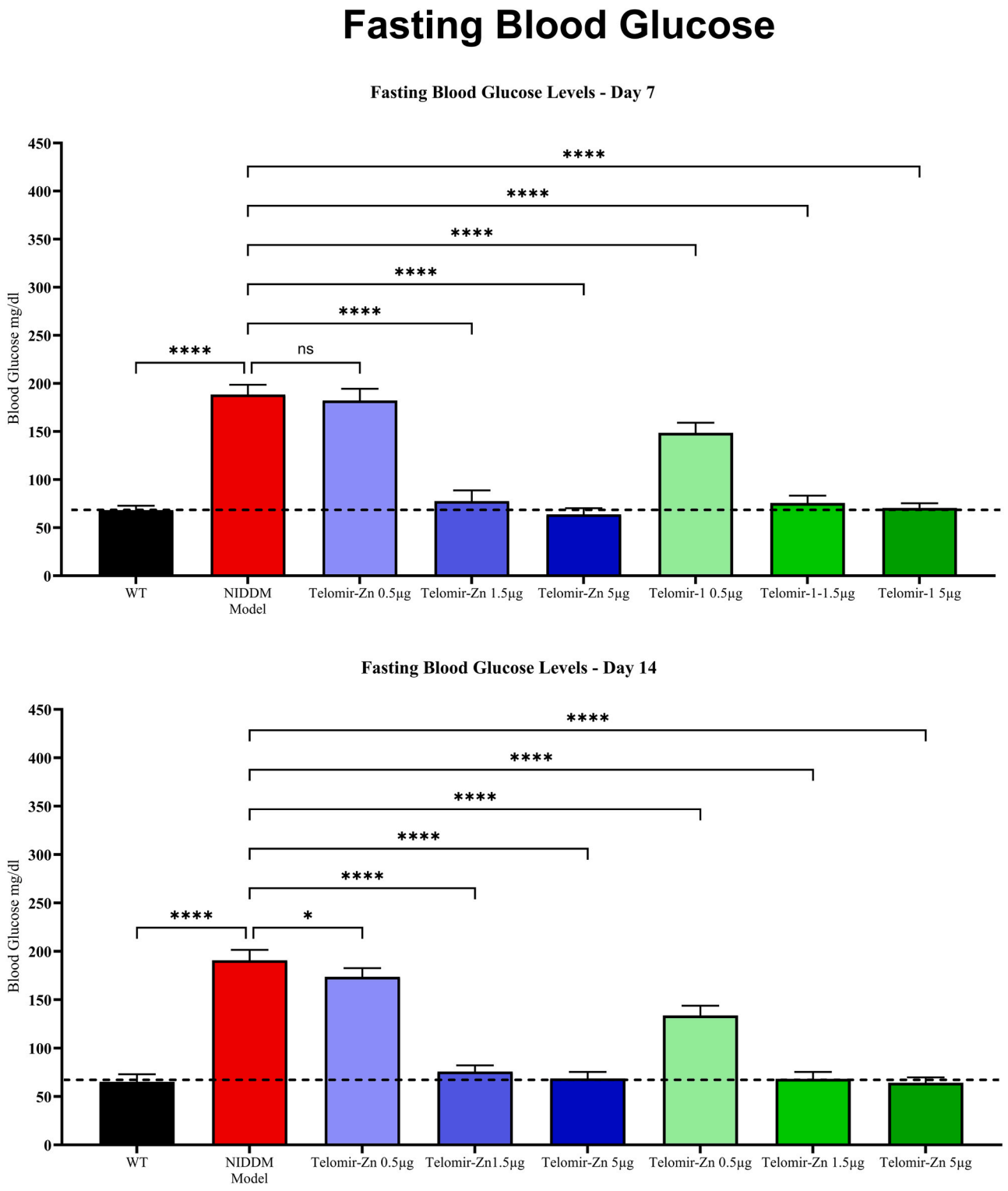

Fig. 2. Fasting blood glucose levels in zebrafish following treatment with Telomir-Zn and Telomir-1. Measurements were obtained at Day 7 (top panel) and Day 14 (bottom panel). Data are presented as mean ± SEM (n = 6 per group). Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test, as described in the Materials and Methods section.

was characterized by severe hyperglycemia, hyperinsulinemia, and impaired glucose tolerance, consistent with insulin resistance. These findings are consistent with previous reports demonstrating that diet-induced obesity in zebrafish reproduces key features of mammalian metabolic disease, including insulin resistance and dysregulated glucose metabolism [8].

One of the notable observations in the present study is the robust reduction in fasting glucose levels and improvement in glucose tolerance following Telomir-Zn treatment. These improvements occurred alongside reductions in fasting insulin concentrations, suggesting that the compound enhances insulin sensitivity rather than simply stimulating insulin secretion. Restoration of insulin sensitivity is a key therapeutic objective in T2DM management, as persistent insulin resistance contributes to progressive β-cell dysfunction and disease progression.

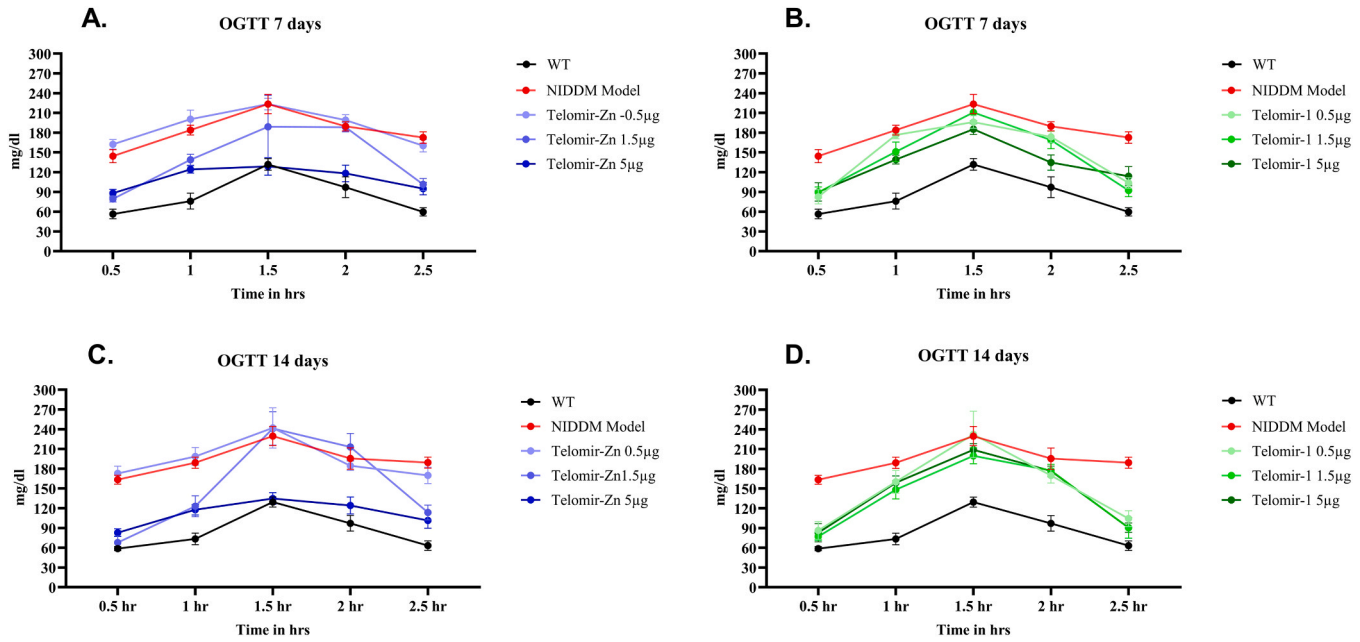

Fig. 3. Oral glucose tolerance test (OGTT) profiles in zebrafish following treatment with Telomir-Zn and Telomir-1. OGTT measurements were obtained at Day 7 (top panels) and Day 14 (bottom panels). Panels A and C represent the Telomir-Zn treatment groups, while panels B and D represent the Telomir-1 treatment groups. Data are presented as mean ± SEM (n = 5–6 per group).

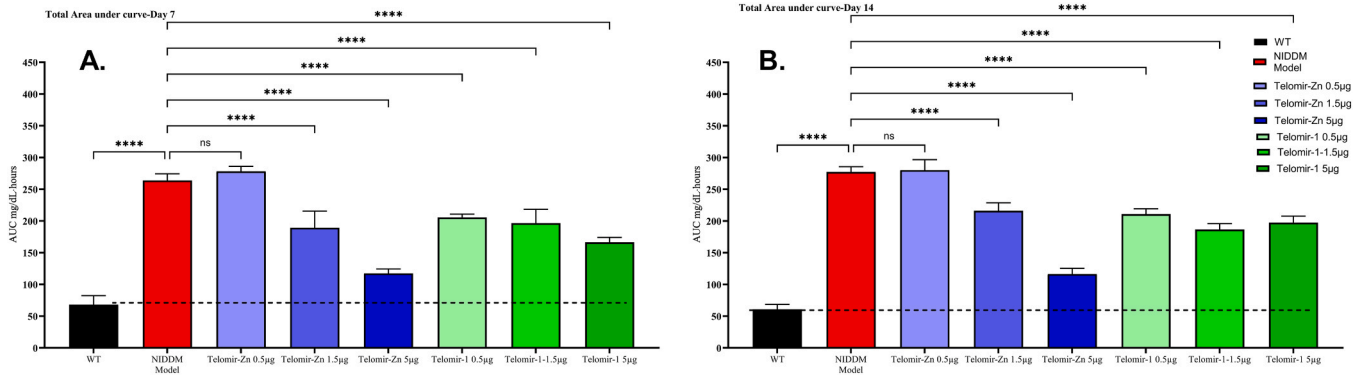

Fig. 4. Area under the curve (AUC) analysis of oral glucose tolerance test (OGTT) responses in zebrafish following treatment with Telomir-Zn and Telomir-1. AUC values were calculated from OGTT profiles at Day 7 (panel A) and Day 14 (panel B). Data are presented as mean ± SEM (n = 5–6 per group).

While the present study focused on functional metabolic outcomes, histopathological evaluation of key organs (pancreas, liver, and adipose tissue) was not performed. In diet-induced zebrafish models of obesity and metabolic dysfunction, high-calorie feeding commonly induces hepatic steatosis, increased visceral adiposity, and compensatory changes in pancreatic islet morphology. Future studies will incorporate histological analyses (e.g., H&E staining, Oil Red O for lipid deposition, and immunohistochemistry for insulin-positive β-cell area) to determine whether Telomir-Zn-mediated improvements in glucose homeostasis and insulin sensitivity are associated with reduced steatosis, normalized adipocyte size, or altered β-cell mass.

Several currently approved classes of antidiabetic drugs target insulin resistance or glucose metabolism through distinct mechanisms. Metformin, the first-line therapy for T2DM, improves glucose homeostasis primarily by suppressing hepatic gluconeogenesis and enhancing peripheral insulin sensitivity through activation of AMP-activated protein kinase (AMPK). Thiazolidinediones (TZDs), such as pioglitazone, act as peroxisome proliferator-activated receptor gamma (PPARγ) agonists that enhance insulin sensitivity in adipose tissue and skeletal muscle [21,22].

More recently introduced classes further expand therapeutic options. Glucagon-like peptide-1 (GLP-1) receptor agonists improve glucose-dependent insulin secretion, suppress glucagon release, slow gastric emptying, and promote satiety, leading to significant weight loss and cardiovascular protection. Sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce renal glucose reabsorption, promoting glucosuria, mild diuresis, and caloric loss, with additional benefits on heart failure, kidney disease, and body weight independent of insulin action [23].

Despite these therapeutic advances, many currently available treatments primarily address downstream metabolic consequences rather than upstream drivers of metabolic dysfunction, such as oxidative stress, mitochondrial dysfunction, and metal dysregulation. Emerging evidence suggests that disturbances in iron metabolism may contribute directly to insulin resistance and T2DM pathogenesis. Elevated iron stores have been associated with impaired insulin sensitivity, while therapeutic phlebotomy or iron reduction has been shown to improve insulin sensitivity in some clinical settings [12].

Excess iron promotes oxidative stress through catalytic redox cycling that generates hydroxyl radicals via Fenton chemistry. These reactive species damage cellular macromolecules and interfere with insulin

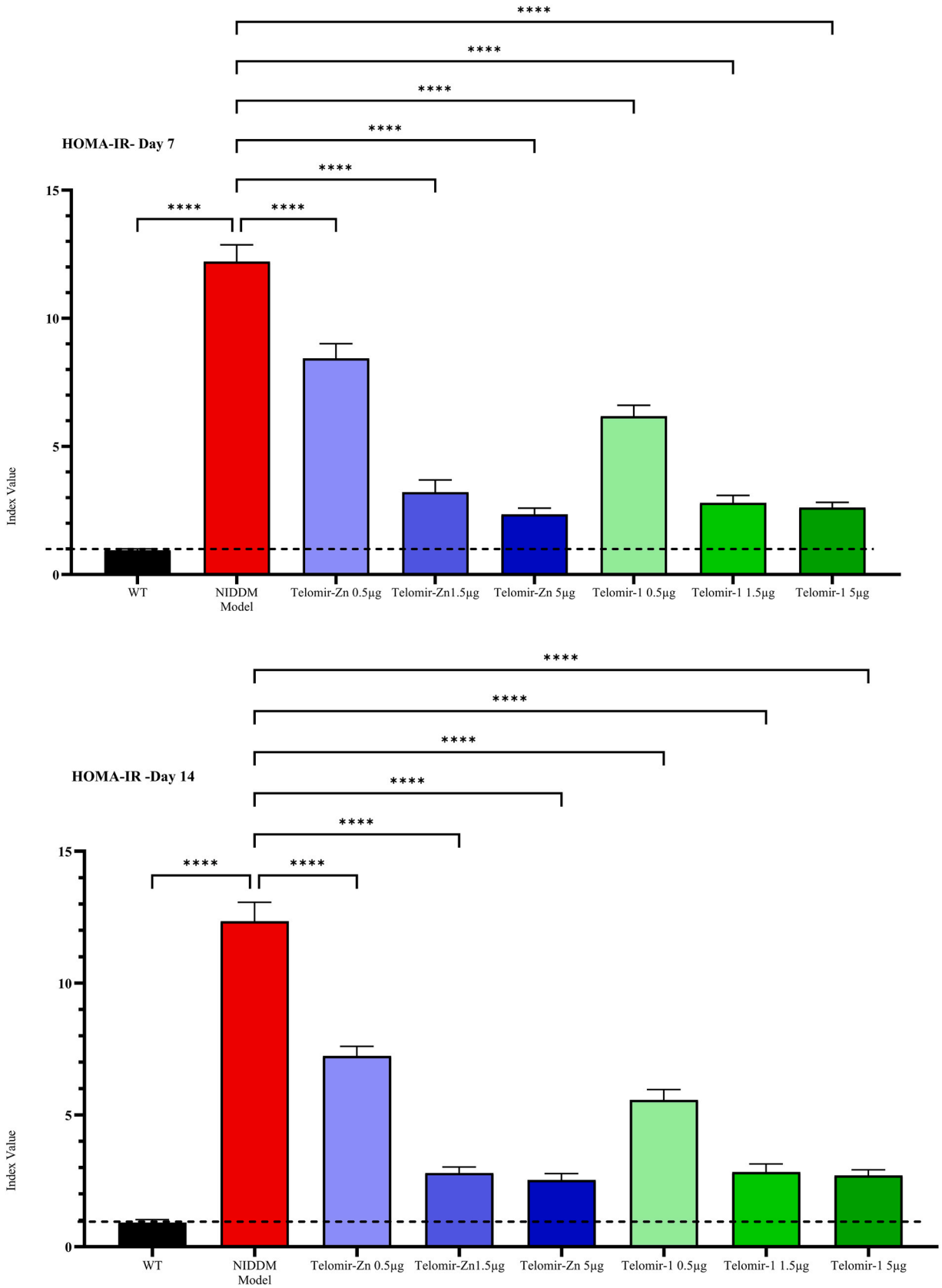

Fig. 5. HOMA-IR values in zebrafish following treatment with Telomir-Zn and Telomir-1. Measurements were obtained at Day 7 (top panel) and Day 14 (bottom panel). Data are presented as mean ± SEM (n = 6 per group). Statistical comparisons were performed using one-way ANOVA followed by Tukey's post-hoc test, as described in the Materials and Methods section.

receptor signaling pathways. In skeletal muscle and liver, oxidative stress can impair insulin-stimulated glucose uptake and disrupt mitochondrial energy metabolism, thereby promoting insulin resistance [14].

The stronger dose-dependent efficacy observed for Telomir-Zn compared with Telomir-1 are consistent with the hypothesis that the zinc complex plays a significant role in mediating the observed metabolic effects. While the ligand alone produced moderate improvements in metabolic parameters, the coordinated zinc complex consistently produced stronger improvements in fasting glucose, OGTT AUC, and insulin resistance.

Zinc is known to act as an important intracellular signaling molecule that influences insulin receptor phosphorylation and downstream signaling cascades. Zinc inhibits protein tyrosine phosphatase 1B (PTP1B), thereby preventing dephosphorylation of the insulin receptor β-subunit and enhancing insulin signaling and GLUT4 translocation. In pancreatic β-cells, zinc plays a critical role in insulin granule formation and maturation by enabling the crystallization of insulin hexamers within secretory granules via the zinc transporter ZnT8 (SLC30A8). Zinc deficiency, or impaired zinc transport, has been consistently associated with defective insulin synthesis, reduced insulin secretion, impaired glucose tolerance, and increased risk of type 2 diabetes [24].

Excess labile iron is known to promote oxidative stress through Fenton chemistry, which can impair insulin signaling. Conversely, zinc supports insulin crystallization, storage, and signaling pathways. Given its design as a zinc-coordinated complex with metal-interacting properties, Telomir-Zn may act by reducing redox-active iron while supplying bioavailable zinc. However, the present study did not directly measure intracellular metal levels or related pathways; therefore, this mechanism remains to be confirmed in future investigations. The stronger and more dose-dependent efficacy of Telomir-Zn compared with the ligand Telomir-1 alone further supports a contribution of the coordinated zinc ion.

In addition to improving insulin sensitivity, Telomir-Zn was previously found to exert beneficial effects on oxidative stress, mitochondrial function, and epigenetic regulation through its metal-modulating activity [19,20]. By exchanging excess intracellular labile iron and copper for bioavailable zinc, Telomir-Zn reduces iron-driven Fenton chemistry, thereby significantly lowering reactive oxygen species (ROS) production while restoring mitochondrial respiration and energy output without promoting cell proliferation. These actions directly counteract the mitochondrial dysfunction and elevated ROS that drive insulin resistance and β-cell stress in type 2 diabetes. Furthermore, because multiple histone lysine demethylases (KDM2, KDM5, and KDM6 families) are iron-dependent Jumonji C-domain enzymes, Telomir-Zn potently inhibits their activity via altered metal availability, leading to epigenetic reprogramming of genes involved in inflammation, insulin signaling, and glucose homeostasis. This mechanism is supported by in vitro data showing Telomir-Zn-mediated inhibition of KDM2A/B, KDM5s, and KDM6A/B [19]. Notably, this epigenetic profile of Telomir-Zn complements the action of metformin, the first-line therapy for type 2 diabetes. In addition to its well-known activation of AMP-activated protein kinase (AMPK), metformin directly inhibits the H3K27me3-specific demethylase KDM6A/UTX in an AMPK-independent manner. This inhibition increases global H3K27me3 levels, reverses aberrant histone methylation patterns, and contributes to metformin's insulin-sensitizing effects and glucose-lowering benefits, including the reversal of metabolic memory in high-fat diet models [25].

From a translational perspective, these findings highlight the potential importance of metal homeostasis as a therapeutic axis in metabolic disease. Targeting redox-active metals such as iron while simultaneously supporting beneficial metal signaling pathways such as zinc-dependent insulin regulation may represent a novel strategy for improving metabolic health.

Although zebrafish models provide valuable insights into metabolic regulation, several limitations should be considered. Zebrafish lack certain aspects of mammalian glucose metabolism, and further studies in rodent models and human systems will be necessary to confirm translational relevance. Additional limitations include the absence of histopathological assessment of metabolic organs and the lack of molecular analyses (e.g., gene expression of insulin signaling, inflammatory, or oxidative stress pathways). These will be addressed in follow-up mammalian (rodent) studies, which will include comprehensive tissue histology, β-cell morphometry, and molecular mechanistic investigations including potential effects on mitochondrial metabolism, Tissue metal (Fe/Zn) quantification, Insulin signaling pathway analysis, oxidative stress pathways, ROS levels and intracellular metal distribution. Although a positive control (e.g., metformin) was not included, the magnitude of metabolic improvement observed with Telomir-Zn indicates strong efficacy in this model. Direct benchmarking against standard agents will be performed in future rodent studies.

Taken together, the present results suggest that Telomir-Zn represents a promising metabolic modulator capable of improving glucose homeostasis and insulin sensitivity. Telomir-Zn represents a mechanistically distinct approach focused on metal homeostasis, which differs from the primary mechanisms of current antidiabetic drugs.

5. Conclusion

The functional benefits of Telomir-Zn observed here provide evidence of efficacy in restoring glucose homeostasis and insulin sensitivity in a vertebrate model of diet-induced metabolic dysfunction. Planned studies in rodent models of type 2 diabetes will evaluate both efficacy and underlying mechanisms, including direct assessment of intracellular labile iron and zinc pools, oxidative stress, and changes in insulin signaling pathways.

CRediT authorship contribution statement

Erez Aminov: Writing – original draft, Supervision, Resources, Project administration, Conceptualization. **Kalaichitra Periyasamy:** Investigation, Formal analysis, Data curation, Conceptualization. **Benin Joseph:** Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Itzchak Angel:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethics Statement

All animal procedures were conducted in accordance with institutional guidelines and were approved by the appropriate Institutional Animal Ethics Committee. The study was performed in compliance with national regulations governing laboratory animal research and adhered to the principles of Good Animal Practice. All procedures were conducted in accordance with the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), India, and the standards of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Declaration of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence tools were used for language editing and formatting assistance. All scientific interpretation, analysis, and conclusions presented in this manuscript were developed solely by the authors.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Erez Aminov is the Chief Executive Officer of Telomir Pharmaceuticals Inc. Itzchak Angel serves as a consultant to Telomir Pharmaceuticals Inc. Some authors are affiliated with or receive compensation from Telomir Pharmaceuticals Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data availability

Data will be made available on request.

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