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Effects of gradient high-field static magnetic fields on diabetic mice

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ABSTRACT

Although 9.4 T magnetic resonance imaging (MRI) has been tested in healthy volunteers, its safety in diabetic patients is unclear. Furthermore, the effects of high static magnetic fields (SMFs), especially gradient vs. uniform fields, have not been investigated in diabetics. Here, we investigated the consequences of exposure to 1.0–9.4 T high SMFs of different gradients (>10 T/m vs. 0–10 T/m) on type 1 diabetic (T1D) and type 2 diabetic (T2D) mice. We found that 14 h of prolonged treatment of gradient (as high as 55.5 T/m) high SMFs (1.0–8.6 T) had negative effects on T1D and T2D mice, including spleen, hepatic, and renal tissue impairment and elevated glycosylated serum protein, blood glucose, inflammation, and anxiety, while 9.4 T quasi-uniform SMFs at 0–10 T/m did not induce the same effects. In regular T1D mice (blood glucose ≥16.7 mmol/L), the >10 T/m gradient high SMFs increased malondialdehyde (P<0.01) and decreased superoxide dismutase (P<0.05). However, in the severe T1D mice (blood glucose ≥30.0 mmol/L), the >10 T/m gradient high SMFs significantly increased tissue damage and reduced survival rate. *In vitro* cellular studies showed that gradient high SMFs increased cellular reactive oxygen species and apoptosis and reduced MS-1 cell number and proliferation. Therefore, this study showed that prolonged exposure to high-field (1.0–8.6 T) >10 T/m gradient SMFs (35–1 380 times higher than that of current clinical MRI) can have negative effects on diabetic mice, especially mice with severe T1D, whereas 9.4 T high SMFs at 0–10 T/m did not produce the same effects, providing important information for the future development and clinical application of SMFs, especially high-field MRI.

Keywords: Type 2 diabetes; Type 1 diabetes; Magnetic resonance imaging (MRI); Gradient static magnetic field; Quasi-uniform static magnetic field

INTRODUCTION

High static magnetic fields (SMFs) are key to improving the quality of magnetic resonance imaging (MRI). Magnetic field flux density for humans has increased from an initial 0.05–0.35 T (Crooks et al., 1982; Smith et al., 1981) to 1.5 and 3.0 T in most hospitals (Abbas et al., 2015), and 9.4 T MRIs have been tested on healthy human volunteers (Atkinson & Thulborn, 2010; Zaiss et al., 2018) and in rhesus monkeys (Chen et al., 2020). The application of high-field MRI and magnetic resonance spectroscopy (MRS) depends heavily on the development of magnetic and imaging techniques, but also on their biosafety. Several recent studies have demonstrated the safety of high SMFs in healthy adult mice. For example, exposure to 2.0–12.0 T high SMFs for four consecutive weeks shows no deleterious effects on healthy mice (Wang et al., 2019). Moreover, neither 2 h of exposure to 3.5–23.0 T (Tian et al., 2019) nor 1 h of exposure to 7.0–33.0 T (Khan et al., 2022; Lv et al., 2022; Tian et al., 2021) induces adverse effects on healthy mice. However, preliminary studies in GIST-T1 tumor-bearing nude mice showed moderate liver

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damage after exposure to 3.7–24.5 T SMFs for 9 h (Tian et al., 2018), indicating that magnetic field flux density, exposure time, and/or animal health may synergistically influence the consequences of high SMF treatment.

Diabetes mellitus (type 1 and type 2), a complex disease characterized by hyperglycemia, has become a severe health threat and global burden (American Diabetes Association, 2013; Hodgson et al., 2022; Lin et al., 2021), especially during the current COVID-19 pandemic (Clotman & Twickler, 2020; Rose & Scibilia, 2021; Sarkisian et al., 2021). Globally, 783 million people are expected to be diagnosed with diabetes by 2045 (Sun et al., 2022). Most diabetic patients have multiple brain, retinal, and renal complications that severely impair their quality of life. In addition to MRI, which is frequently used in Diabetes Control and Complications Trials (DCCT) (Biessels & Reijmer, 2014; Geijselaers et al., 2015), magnetic fields are also suggested to have treatment potential in diabetes. Recent studies have shown that 3 mT moderate SMF combined with an electric field or 100 mT moderate SMF alone can reduce blood glucose and alleviate diabetic complications in T2D mice (Carter et al., 2020; Yu et al., 2021). However, the effects of high SMFs on T2D are unclear, and there are no reports on T1D.

Here, we used a superconducting magnet to provide a 1.0–9.4 T SMF environment in a vertically upward direction (9.4 T in the center, descending fields with various gradients off-center) for 14 h to investigate the effects of quasi-uniform (near homogeneous, ∇B=0–10 T/m) and gradient (∇B>10 T/m) SMF environments on three diabetic mouse models. As multiple studies have shown that shorter exposure (1–2 h) of up to 33 T SMFs does not negatively affect healthy mice, we explored the healthy threshold by combining disease mouse models and longer than usual treatment times. We found that >10 T/m gradient SMFs generated deleterious effects in both T1D and T2D mice, especially the more severe T1D mice. In contrast, 0–10 T/m quasi-uniform 9.4 T SMFs, the highest magnetic field in our experiments, had no deleterious effects on diabetic mice.

MATERIALS AND METHODS

Animal model

Five-week-old male specific-pathogen-free (SPF) C57BL/6J mice were obtained from Nanjing GemPharmatech Co., Ltd., China. All protocols involving animals were approved by the Association of Laboratory Animal Sciences at Anhui Medical University (approval No. LLSC20211057) and were carried out in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication, 8th Edition, 2011).

To create the T2D mouse model, the mice were given a high fat diet (HFD) for six weeks and intraperitoneally injected with 45 mg/kg streptozotocin (STZ, 0.01 mol/L citrate buffer, pH 4.2) for three consecutive days. The model was considered successfully established in mice with fasting blood glucose levels of ≥11.1 mmol/L (Yu et al., 2021).

We induced two different T1D mouse models by an intraperitoneal injection of STZ in 0.01 mol/L citrate buffer. For regular T1D, STZ (50 mg/kg) was administered in mice for five consecutive days, with a fasting blood glucose level of ≥16.7 mM considered successfully established (Furman, 2015); for severe T1D, a single injection of STZ (150 mg/kg) was used (Feng et al., 2017), with a fasting blood glucose level of ≥30.0 mM considered successfully established.

In total, 194 mice were investigated in three experiments (Supplementary Figure S1), mostly divided into five groups: (a) Healthy group: mice without any STZ intraperitoneal injection; (b) Sham 1 group: diabetic mice treated with “fake” magnetic conditions, placed at the same positions as group (c) within the superconducting magnet; (c) Gradient SMF group: diabetic mice under gradient SMF conditions (∇B>10 T/m); (d) Sham 2 group: diabetic mice treated with “fake” magnetic conditions, placed at the same positions as group (e) within the superconducting magnet; (e) Quasi-uniform SMF group: diabetic mice treated with quasi-uniform SMF conditions (∇B=0–10 T/m).

9.4 T superconducting magnet exposure

The superconducting magnet with a 100 mm diameter room-temperature bore (Xi’an Superconducting Magnet Technology, China) can deliver a vertical SMF of up to 10 T in the center and gradient SMFs off-center (Figure 1). We set the maximum SMF in the center to 9.4 T, as described previously (Yang et al., 2021). To ensure accurate control, we established “sham groups” that mimicked the environmental conditions of the SMF exposure groups. We created two identical exposure systems, with the same dimensions and air circulation and in the same room. The incubation systems contained double-layer non-magnetic stainless-steel cylinders with an inner diameter of 87 mm and an outer diameter of 99 mm (Supplementary Figure S2). We designed and constructed two coaxial non-magnetic stainless-steel mouse and cell exposure devices (81 mm diameter, 15 layers, 900 mm total height) (Supplementary Figure S2D). A PT100 near the sample was used as a temperature sensor connected to a temperature display to monitor sample temperature. The temperature of the samples was controlled by water in the space between the inner and outer tubes. To ensure the mice received sufficient oxygen, a pump was used to blow air into the cylinder bore at 450 L/min. For cellular assays, 5% CO_2 was introduced through the air hole at the top and temperature was maintained at 37 °C. The mice and cells in the sham groups were placed in identical replica settings as the SMF group, and the experiments were performed side-by-side.

For the mouse experiments, we chose layers 2 to 14, with magnetic field induction (B) ranging from 1.0 to 9.4 T and magnetic field gradient (∇B) ranging from 0 to 55.5 T/m (Figure 1). For cellular assays, cells were placed at layers 5 and 11 for the gradient condition and layer 8 for the quasi-uniform condition. For *in vitro* and *in vivo* experiments, the SMF exposure time was 14 h in total, including increasing field for 2 h, decreasing field for 1.5 h, and constant field for 10.5 h (from 1800h to 0830h overnight).

Behavioral tests

An open field test (OFT) was used to evaluate the locomotion and exploration activities of mice. Briefly, the apparatus contained a white Plexiglas box (L×W×H: 100 cm×100 cm×40 cm) divided into four identical square areas, which can accommodate four mice simultaneously. Mice were placed in the center of the square and allowed to freely explore the open field for 6 min (Supplementary Figure S3). Their movements were recorded using a camera mounted on the top center and analyzed automatically using the ANY-Maze Video Tracking System (Stoelting, USA).

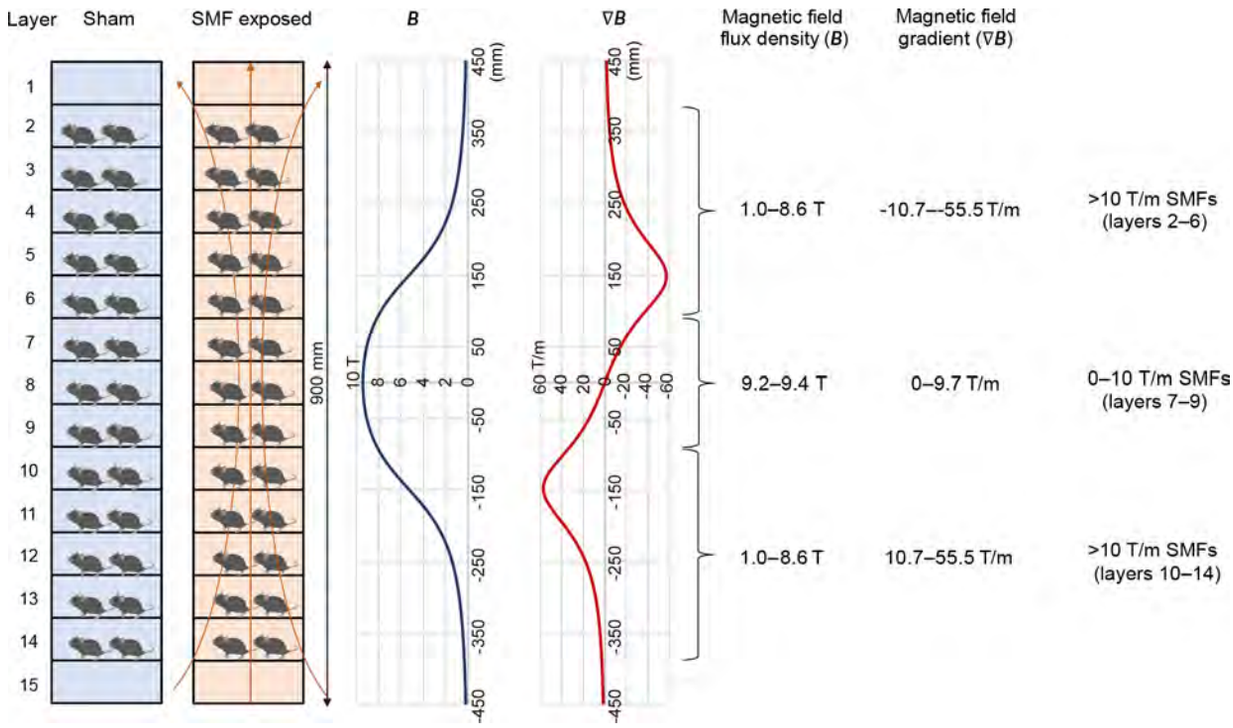

Figure 1 Illustration of 9.4 T superconducting magnet experimental set up

Magnetic field flux density (*B*) and magnetic gradient (∇*B*) are shown.

Complete blood count and blood biochemical analysis

Mice were sacrificed the day after SMF treatment and blood was obtained by 1% pentobarbital sodium anesthesia at the end of the experiment. Blood samples (200 μL) were mixed with 0.15% (M/V) EDTA-K_2-$2H_2O$ anticoagulant immediately after collection and subjected to complete blood count analysis. The remaining blood samples were placed in 1.5 mL centrifuge tubes and centrifuged at 4 ℃ and 3 500 ×*g* for 15 min to collect serum, which was analyzed using an automated biochemical analyzer (Olympus, Japan).

Enzyme activity assay

The tissue levels of superoxide dismutase (SOD) and malondialdehyde (MDA) were assayed using commercial standard kits (Aimeng Youning, China). Absorbance rates were recorded by a spectrophotometer at 450 nm for both SOD and MDA. The SOD and MDA results are reported in U/mg protein and nmol/mg protein, respectively. Protein content was assayed using a BCA protein quantification kit (Vazyme Biotech, China).

Histomorphological analysis

For hematoxylin and eosin (H&E) and Masson trichrome staining, mouse tissues and organs were fixed in 4% paraformaldehyde for 24 h, then embedded in paraffin and sectioned into 5 μm slices using a semiautomated rotary microtome (Leica Biosytems RM2245, Germany). Tissue sections were then stained with H&E and Masson trichrome and imaged using a Nikon TS100 microscope (Nikon, Japan). The H&E and Masson trichrome stains were assessed by independent researchers in a blinded manner.

Cell number count and reactive oxygen species (ROS) detection

The murine MS-1 (Mile Sven 1) pancreatic islet endothelial cell line was obtained from the American Type Culture Collection (ATCC, CRL-2279) and cultured in Dulbecco's Modified Eagle Medium (DMEM) (Shanghai QiDa Biotechnology, China) supplemented with 10% fetal bovine serum (FBS). The MS-1 cells were seeded in 35 mm plates and cultured for one day in a regular CO_2 cell incubator. The medium was replaced with high glucose (HG, 50 mmol/L) DMEM and the cells were then exposed to sham 1, gradient SMF (6.1 T, ±55.5 T/m), sham 2, or 9.4 T uniform SMF (9.4 T, 0 T/m). Cell counts and intracellular ROS levels were then measured by flow cytometry (Beckman Coulter, USA).

Immunohistochemical analysis

For immunohistochemical analysis of insulin (#66198-1-Ig, Proteintech, USA), interleukin 6 (IL-6) (#21865-1-AP, Proteintech, USA), and tumor necrosis factor α (TNFα) (BA0131, Bosterbio, China) in severe T1D mice, all steps were performed as previously described (Yu et al., 2021). Images were obtained using a Nikon TS100 microscope (Nikon, Japan) and image intensity was calculated by ImageJ software (version 1.49j) (NIH, USA). At least three independent slides per group were analyzed in a blinded manner.

Western blot analysis

Proteins from the MS-1 cells were extracted using cell lysis buffer with inhibitors for western blot analysis. All proteins were separated by 10%–15% sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were blocked with 5% nonfat milk and incubated with different primary antibodies (PARP (#9532T, 1:1000, CST, USA), BAX (#5023S, 1:1000, CST, USA), PCNA (#13110S, 1:1000, CST, USA), and GAPDH (#HC301-01, 1:4000, TransGen Biotech, China)) at 4 °C overnight, then incubated with the corresponding secondary antibodies for 1 h at room temperature. The immunocomplexes were detected using an ECL system (PerkinElmer, USA). All experiments were repeated at least three times.

Statistical analysis

Data are expressed as mean±standard deviation (*SD*). Normality of data was assessed by the Shapiro-Wilk test using GraphPad Prism v7.0. For normally distributed data, unpaired *t*-tests were used to evaluate differences between groups. For non-normally distributed data, the Mann-Whitney *U* tests were used. $P<0.05$ was considered statistically significant. All experiments were performed blinded or repeated by independent researchers. Those who performed the experiments after SMF exposure and/or analyzed the data were not aware of mouse exposure conditions.

RESULTS

Gradient SMFs, but not quasi-uniform SMFs, increased blood glucose in T1D/T2D mice and mortality in severe T1D mice

To obtain information on high SMFs with different parameters, we used vertical superconducting magnets, which provide quasi-uniform 9.2–9.4 T SMFs in the center and 1.0–8.6 T gradient SMFs off-center (Figure 1). We examined T2D (fasting blood glucose≥11.1 mmol/L) and T1D mouse models, including regular T1D (fasting blood glucose≥16.7 mmol/L) and severe T1D (fasting blood glucose≥30.0 mmol/L) (Supplementary Figure S1). Blood glucose and glycated serum protein (GSP) measurements after 14 h of exposure revealed differences between the gradient SMF and sham groups (Figure 2A, B) in both T2D and T1D mice. In contrast, quasi-uniform 9.4 T SMFs did not induce such effects.

Gradient SMF treatment triggered serious hypoglycemia in some severe T1D mice, with blood glucose levels dropping to 1.3 mmol/L in three mice (Figure 2A). Although gradient SMF treatment did not lead to differences in GSP levels in severe T1D mice ($P>0.05$) (Figure 2B), insulin secretion was reduced ($P<0.001$) and was more pronounced than in regular T1D and T2D mice (Figure 2C; Supplementary Figure S3). In addition, gradient SMFs not only resulted in decreased total travelled distance, total average speed, number of entries, time spent, and movement speed in the center zone of the OFT in severe T1D mice (Supplementary Figures S4, S5), indicating decreased locomotion and exploration activities, but also unexpectedly caused mouse lethality (Figure 2D; Supplementary Figure S6). Notably, all dead mice were in the >20 T/m gradient group, with no mortality found in the sham or 0–10 T/m SMF groups (Figure 2D). In addition, no obvious changes in the OFT were observed in the T2D and regular T1D mice (Supplementary Figure S5), consistent with the unimpaired survival of regular T1D and T2D mice (Figure 2D).

Gradient SMFs exacerbated physiological and pathological abnormalities in diabetic mice

To monitor the health of diabetic mice treated with high SMFs, we performed blood tests and tissue examinations. Gradient SMF-treated mice had significantly increased uric acid (UA) levels, a blood biochemical indicator of kidney function, in all three diabetic groups (Figure 3A). Furthermore, based on H&E staining, gradient SMFs caused obvious histomorphological changes in the liver, kidney, and spleen. Specifically, gradient SMFs induced more pronounced glomerular vacuolation with irregular morphology and atrophy, hepatocyte injury, and blurred red-white medullary demarcation in the spleen, especially in severe T1D mice (Figure 3B). In contrast, quasi-uniform SMF treatment showed no such effects. Complete blood count indicators (including white blood cell (WBC), lymphocyte (Lymph), granulocyte (Gran), red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and platelet (PLT)), blood biochemical indicators (including alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (T-BIL), blood urea nitrogen (BUN), creatinine (CREA), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), iron (Fe), and calcium (Ca)), and organ histomorphological staining (heart, lung, and pancreas) were examined in all three diabetic groups (Supplementary Figures S7–S12).

To clarify the effects of gradient SMF treatment in severe T1D mice, we also examined levels of inflammatory cytokines IL-6 and TNFα in the liver, kidney, and spleen. Results showed that both IL-6 and TNFα were significantly increased in the liver, kidney, and spleen of severe T1D mice after gradient SMF exposure, but not after quasi-uniform SMF exposure (Figure 4A–D).

Gradient SMFs increased oxidative stress in diabetic mice and MS-1 cells

To further investigate the possible mechanism by which gradient SMFs exacerbate physiological and pathological abnormalities, we examined the oxidative stress status in the liver, kidney, and spleen using oxidative stress indicators SOD and MDA (Figure 5A, B; Supplementary Figure S13). Results showed that SOD levels were decreased (Figure 5A) and MDA levels were increased (Figure 5B) in the kidney tissue of T1D mice after gradient SMF exposure. In contrast, no significant changes were observed in T2D mice or from quasi-uniform SMF exposure (Figure 5A, B).

Islet endothelial cells are essential for the delivery of oxygen, cytokines, and secretory signals, and induce insulin gene expression during pancreatic islet development (Lammert et al., 2001), whose dysfunction contributes to diabetic macrovascular and microvascular complications (Hogan et al., 2017). Here, we used MS-1 cells treated with high glucose to explore the effects of SMFs *in vitro*. Our results showed that gradient SMFs increased cellular ROS ($P<0.01$) and cleaved-PARP ($P<0.05$) and BAX ($P<0.05$) protein expression, and decreased cell number ($P<0.05$) and PCNA expression, in the high glucose-treated MS-1 cells (Figure 5C, D), indicating that gradient SMFs generate cytotoxicity and cell apoptosis through oxidative stress (Figure 6).

DISCUSSION

Our results showed that exposure to 0–10 T/m SMFs at 9.4 T for 14 h did not produce noticeable damage in the three types of diabetic mice, but gradient (>10 T/m) SMF exposure caused harmful effects in diabetic mice, especially severe T1D mice, which may be correlated to oxidative stress and inflammation induced by persistent hyperglycemia (Figure 6).

Gradient SMFs are known to produce more pronounced biological effects related to magnetic forces acting on subcellular components and biomolecules (Zablotskii et al., 2016, 2018). Previous studies on the safety of high SMF exposure in mice (>20 T and 30 T) used equivalent magnetic field gradients as this study, but primarily in healthy mice, thus reporting no detrimental effects (Khan et al., 2022; Lv et al., 2022; Tian et al., 2018, 2019, 2021). Our results demonstrated

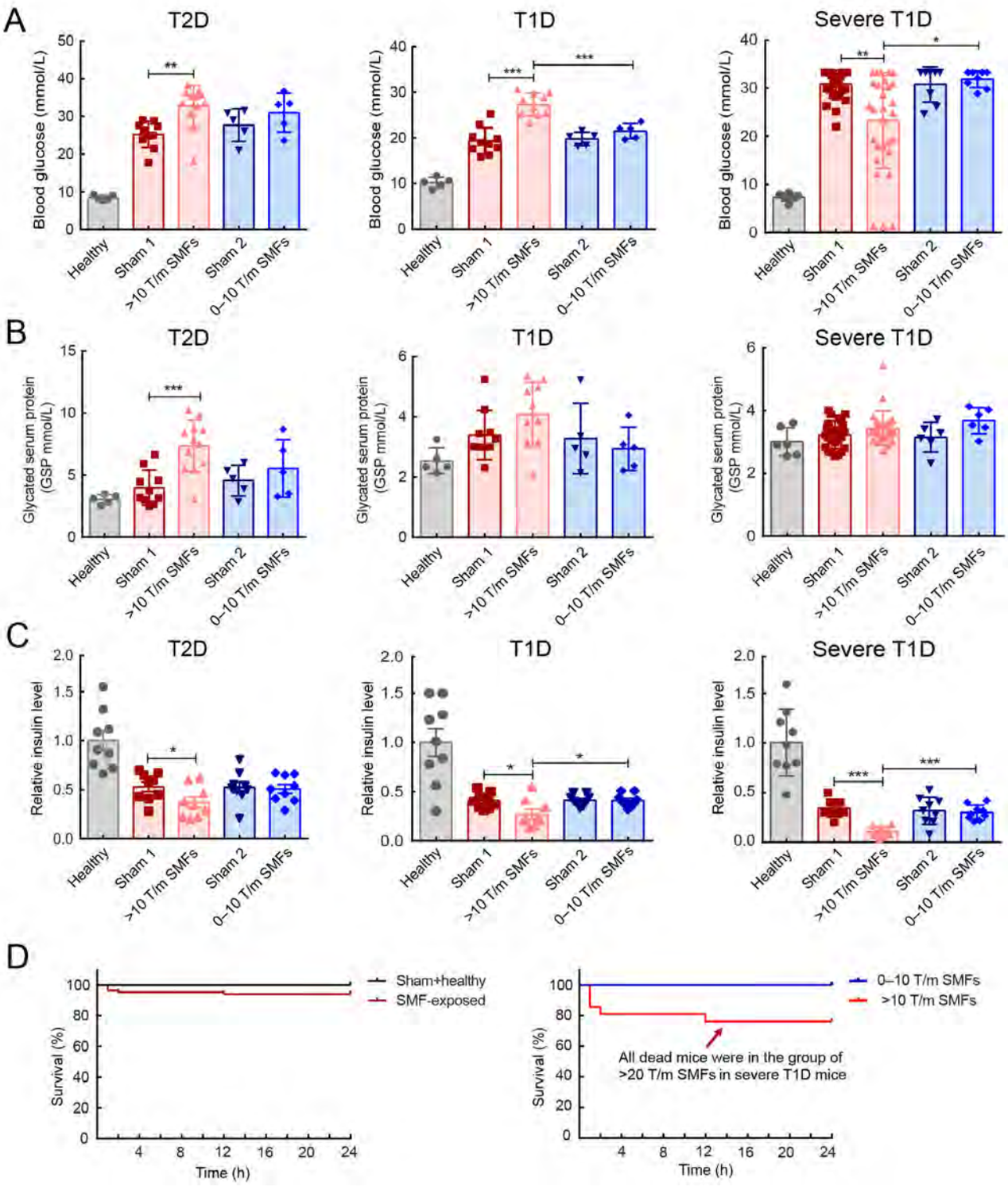

Figure 2 Exposure to high-gradient SMFs increased blood glucose levels in T1D and T2D mice and mortality in severe T1D mice

A, B: Blood glucose (A) and glycated serum protein (GSP)(B) levels were examined in healthy, T2D, regular T1D, and severe T1D mice with or without SMF treatment. C: Relative insulin levels in islets (n=3 islets/mouse from n=3 mice/group) of three types of diabetic mice. D: Left: Survival rate curves of healthy and all diabetic mice with or without SMF treatment. Black line represents healthy, sham 1, and sham 2 groups (n=108), none of which died during our experiments. Dark red line represents diabetic mice (all types) after high SMF exposure (n=86). Right: survival rate curves of all three types of diabetic mice after >10 T/m high-gradient (n=65) vs. 0–10 T/m (n=21) SMF treatment. All dead mice (five in total) were in the severe T1D group exposed to >20 T/m high-gradient SMFs. *: P<0.05; **: P<0.01; ***: P<0.001.

that, although the overall effects of >10 T/m gradient SMFs were not that severe in regular T1D and T2D mice, blood glucose levels were elevated and insulin levels were decreased, likely due to oxidative stress-induced dysfunction of pancreatic islets. In addition, as glycemic control can be difficult in patients with severe T1D (average blood glucose ≥ 22.2 mmol/L (de Jesus Gomes et al., 2019)), leading to repeated and occasionally fatal hypoglycemic episodes (Fujita

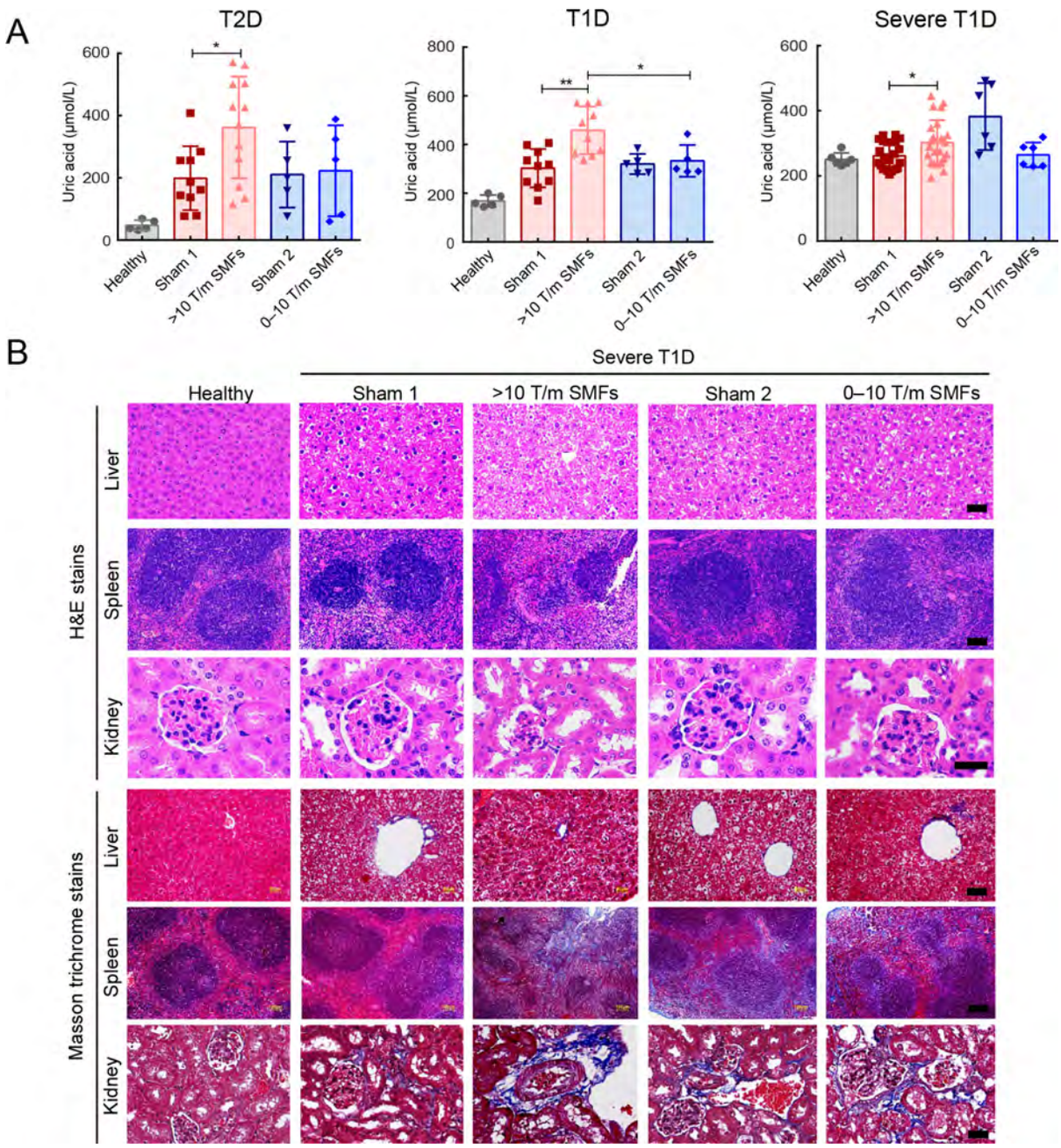

Figure 3 High-gradient SMFs exacerbated physiological and pathological abnormalities in diabetic mice

A: Uric acid levels and B: representative images of H&E- and Masson trichrome-stained sections of liver, spleen, and kidney in healthy vs. severe T1D mice treated with or without SMFs. Scale bar: 50 μm or 100 μm. *: $P<0.05$; **: $P<0.01$.

et al., 2018), causing 4%–10% of patient deaths (Patterson et al., 2007), it is not surprising that prolonged treatment with >10 T/m gradient SMFs induced hypoglycemic episodes and detrimental effects in severe T1D mice, more pronounced than in regular T1D and T2D mice.

Oxidative stress is recognized as a contributing factor to pancreatic β-cell failure, insulin resistance, and secondary complications in peripheral tissue (Chen et al., 2015). Various studies have shown that SMFs can affect ROS levels in biological systems, potentially related to magnetic field flux density and gradient (Wang & Zhang, 2017; Zhang et al., 2017). In general, lower intensities and gradients tend to decrease ROS levels, while higher fields and gradients tend to increase ROS levels (Zhang et al., 2017). In this study, we examined oxidative stress status by measuring oxidative indicators, SOD and MDA, and ROS levels. Results showed that SOD was decreased and MDA was increased in the tissues of diabetic mice treated with gradient SMFs, and higher ROS levels were observed in the high glucose-treated MS-1 cells. These results indicate that gradient SMF treatment can increase hyperglycemia-induced oxidative stress, further exacerbating inflammation and other complications.

However, several studies have shown that weak to moderate SMFs can have some positive effects in diabetic mice. For example, exposure to a static electric field (7 kV/m) combined with 3 mT SMF (Carter et al., 2020) and downward SMF of 100 mT (Yu et al., 2021) can have positive effects on T2D mice. Furthermore, exposure to 2.8–476.7 mT heterogenous SMFs for 12 weeks can significantly alleviate hyperglycemia in STZ-induced T1D mice (László et al., 2011).

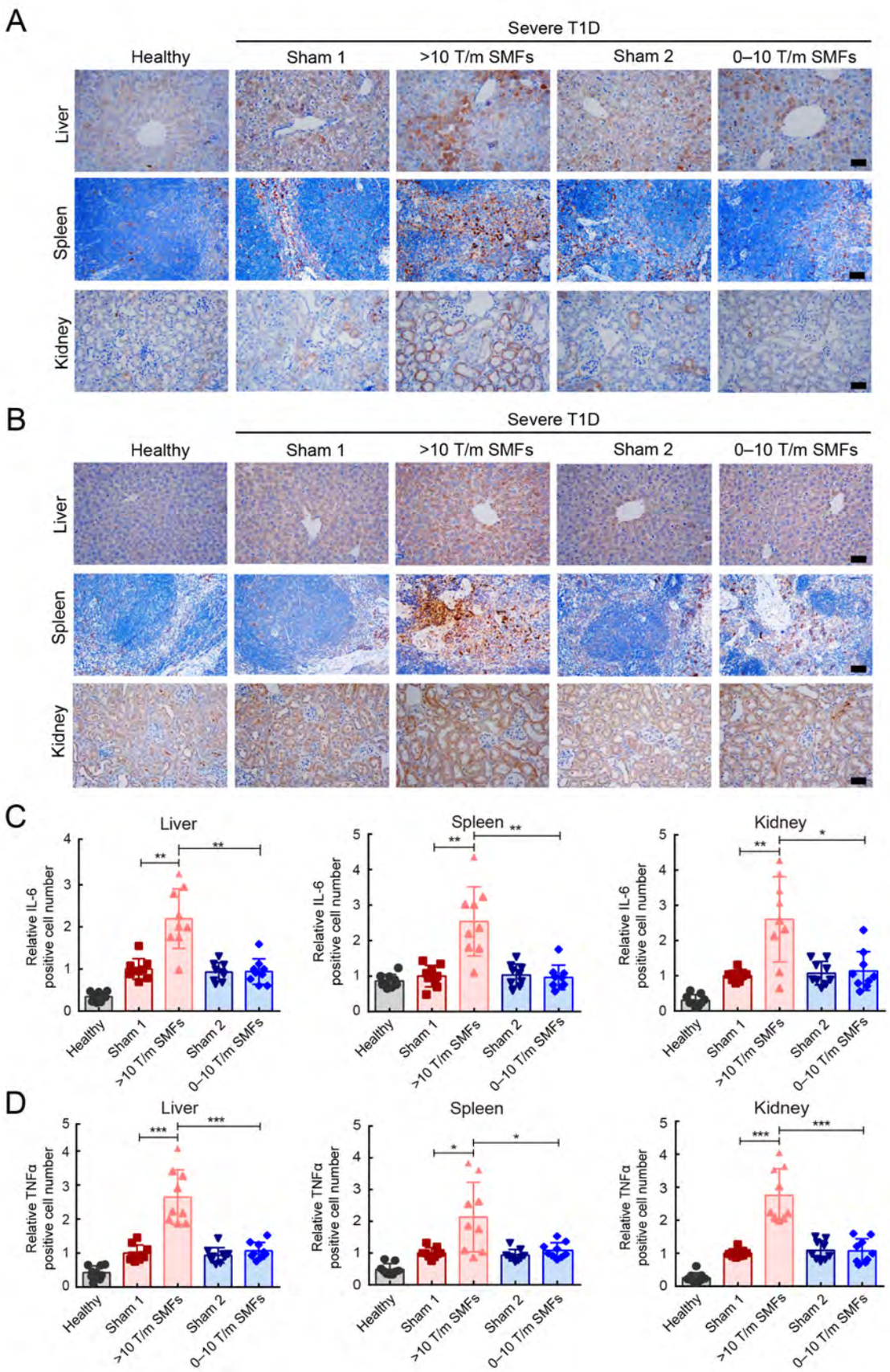

Figure 4 High-gradient SMFs increased inflammation in severe T1D mice

A, B: Representative images of immunohistochemical staining (in brown) for IL-6 (A) and TNFα (B) in liver, spleen, and kidney of severe T1D mice. Scale bar: 50 μm. C, D: Relative IL-6- (C) and TNFα-positive (D) cell number in liver, spleen, and kidney of healthy vs. severe T1D mice treated with or without SMFs. *: P<0.05; **: P<0.01; ***: P<0.001.

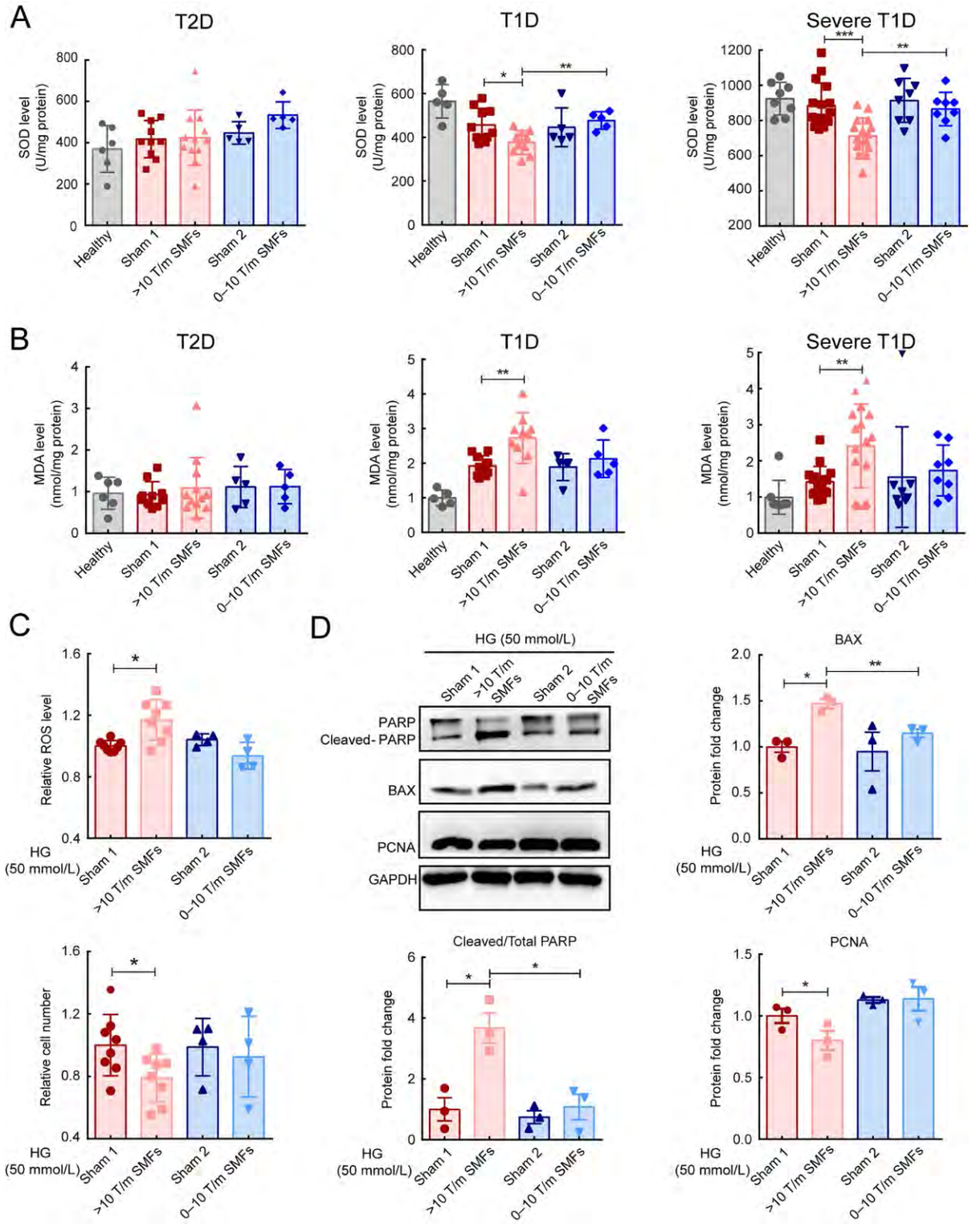

Figure 5 Exposure to high-gradient SMFs increased oxidative stress state in diabetic mice and MS-1 cells

A, B: SOD (A) and MDA (B) levels in kidney tissues of healthy vs. diabetic mice treated with or without SMFs. C: ROS level and cell number of high glucose (HG, 50 mmol/L)-treated MS-1 cells treated with or without SMFs. SMF exposure time was 14 h in total. D: Protein fold-change and representative results of western blot analysis of PARP, cleaved PARP, BAX, PCNA, and GAPDH proteins in MS-1 cells. *: P<0.05; **: P<0.01; ***: P<0.001.

These studies also showed that lower SMFs (<0.5 T) can decrease ROS levels, in contrast to our findings on high-gradient SMFs. Therefore, different intensities and gradients of SMFs may induce differential effects on oxidative stress, leading to different consequences at the cellular and organismal levels.

Our study has several limitations. First, restricted by the aperture size of the superconducting magnets, small sample size is the main limitation of our study. Second, our exposure time (~14 h) was much longer than that in hospital MRI examinations (~0.5 h), and it is unclear whether shorter time

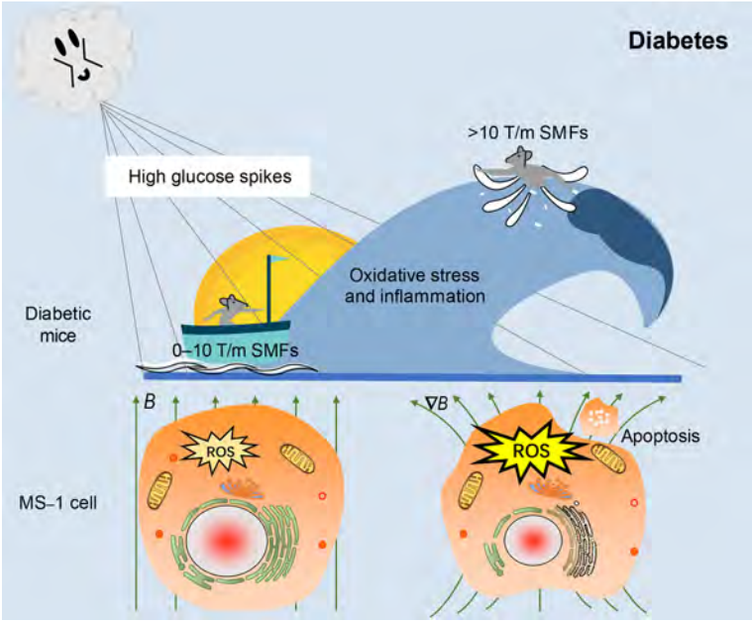

Figure 6 Schematic of detrimental effects induced by gradient high-field static magnetic fields and high glucose levels through oxidative stress

points can cause similar harmful effects. In addition, we did not investigate the effects of pulsed magnetic fields, which are also used in MRI and may cause potential health risks. Third, although emerging data suggest that different SMF orientations can induce different biological effects (Yu et al., 2021; Zhang et al., 2017) and most SMFs in hospital MRI examinations are horizontal, we only used the vertical direction due to equipment limitations. Fourth, while our results should help future human studies, they cannot be directly translated to humans as we only investigated diabetic mice. Therefore, greater attention should be paid to safety in other severe pathological conditions in future studies. Lastly, the mechanism of increased oxidative stress and induced diabetic complications remains to be investigated.

Our results showed that although 0–10 T/m, 9.4 T high SMF exposure for 14 h was safe for all three types of diabetic mice, gradient (>10 T/m) high-field (1.0–8.6 T) SMFs were potentially harmful, especially in mice with severe T1D. These results not only have important implications for the future development of high-resolution MRI machines, but also have cautionary implications for the application of gradient high SMFs in severe diabetic patients. Thus, greater efforts are needed to help establish guidelines for occupational and patient exposure to high SMFs.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

X.Z.: Conceptualization, methodology, supervision, writing–original draft, writing–review & editing. B.Y.: Conceptualization, formal analysis, investigation, methodology, software, visualization, writing–original draft, writing–review & editing. C.S., C.L.F., J.Z., Y.M.Z., Y.W., L.Z., X.M.J., X.F.T., G.F.C., and W.L.C.: Methodology, resources, writing–review & editing. V.Z. and H.W.: Resources, data curation, investigation, writing–review & editing. All authors read and approved the final version of the manuscript.

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