Review

Effects of Static Magnetic Fields on Metabolic Diseases

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Abstract: Metabolic diseases encompass a range of disorders resulting from disruptions in amino acid, glucose, lipid, or energy homeostasis. In recent years, there has been increasing recognition among researchers that static magnetic fields (SMFs) can have diverse effects on certain metabolic diseases. Cellular and animal studies indicate that SMFs elicit markedly different responses in animals, depending on whether they are healthy or have pathological conditions. Notably, several studies have reported that SMFs with specific parameters could have beneficial effects in mice with diabetes, fatty liver disease, and cancer. However, the safety threshold for SMF exposure appears to be significantly lower in mice with severe metabolic diseases, such as severe diabetes or alcoholic liver disease, compared to healthy mice. Furthermore, the SMF direction is also an indispensable factor in regulating pathological conditions involving cell proliferation. This review aims to summarize the impact of SMFs on prevalent metabolic diseases, including diabetes, fatty liver disease, and cancer, explore their potential mechanisms, and address the factors contributing to the inconsistent findings in the literature. The goal is to provide a foundation for the future development of SMFs as non-invasive, highly penetrative physical approaches for diagnosing and treating metabolic disorders.

Keywords: metabolic diseases; static magnetic fields (SMFs); diabetes; fatty liver disease; cancer; magnetic field effects

1. Introduction

Metabolic diseases, including obesity, diabetes, non-alcoholic fatty liver disease (NAFLD), and cancer, are increasingly becoming a significant threat to public health worldwide, contributing to the growing burden on global healthcare systems [1]. As of 2021, diabetes affected approximately 536.6 million people aged 20 to 79, with prevalence of 10.5%, and this figure has been increasing annually [2]. Concurrently, metabolic-associated fatty liver disease (MAFLD) affects approximately 25–30% of the global population, with its prevalence closely following the increasing rates of obesity and type 2 diabetes (T2D) [3,4]. Furthermore, cancer remains one of the leading causes of death worldwide, with China currently holding the highest incidence and mortality rates [5].

In recent years, numerous studies have demonstrated that static magnetic fields (SMFs) can serve as non-invasive, highly penetrating, and safe physical modalities with promising therapeutic potential for various metabolic diseases, including diabetes, fatty liver disease and cancer. For instance, Yu et al. found that a vertically downward SMF of approximately 0.1 T effectively mitigated the progression of hyperglycemia, fatty liver, weight gain, and tissue injury in high-fat diet (HFD) and streptozotocin (STZ)-induced T2D mice [6]. Similarly, Carter et al. reported that the combination of a 3 mT SMF and an electrostatic field significantly improved T2D across three different mouse models [7]. Furthermore, Wang et al. recently found that SMFs can enhance the anti-diabetic effects of intermittent fasting in both moderate and severe diabetic mice [8]. However, some studies have also highlighted a lack of efficacy or even adverse effects of SMFs in regulating blood glucose levels [9].

It has become increasingly clear that the biological effects of SMFs are not solely dependent on SMF parameters, such as intensity, gradient, direction, and treatment duration. They are also influenced by the physiological and pathological conditions of the organism. This review aims to summarize the current experimental evidence regarding the effects of SMFs on both healthy and diseased states. Additionally, we will provide an overview of studies supporting or challenging the therapeutic potential of SMFs for specific metabolic diseases, alongside a mechanistic analysis. Our objective is to offer an updated overview for researchers who are

interested in investigating the potential clinical applications of static magnetic fields in diagnosing and treating metabolic disorders.

2. Magnetic Fields and Life

The Earth itself acts as a vast, yet relatively weak magnet, with a surface field intensity of only 0.5 Gs (1 Gs = 10^{-4} T). People are increasingly aware that all life, including humans, thrives within this pervasive and relatively weak magnetic environment.

Magnetic fields are fundamental to life and health, spanning an extensive range of intensities across 15–16 orders of magnitude. Human bodies generate and are affected by various magnetic fields, from the minuscule electromagnetic fields in neurons and heart, which are billions of times weaker than the Earth's magnetic field—to those created by household appliances, high-voltage power lines, and mobile electronic devices. The faint magnetic signatures of human bodies can be detected using sensitive magnetic sensors by scanning the body surface [10]. The most common examples are magnetocardiography and magnetoencephalography. For instance, Shen et al. utilized quantum sensors to detect weak magnetic fields generated by the brain and heart, showcasing their potential for macroscopic detection of subtle biomagnetic signals emanating from the human body [11].

Magnetic resonance imaging (MRI) scanners, which typically operate at field strengths of 1.5 T or 3 T, are widely used in clinical diagnostics, offering magnetic fields 10,000 to 60,000 times stronger than the Earth's magnetic field [12]. Driven by the demand for higher resolution images in specialized applications, the MRI systems are continuously being improved to achieve higher field intensities. Numerous MRI machines with magnetic fields exceeding 7 T are now in use worldwide, enabling scans with unprecedented clarity. For instance, a 10.5 T MRI significantly improves the signal-to-noise ratio and enhances susceptibility contrast [13]. Additionally, Feinberg et al. introduced a next-generation 7 T MRI scanner specifically designed for ultra-high-resolution human brain imaging, further demonstrating the potential of MRI machines with field strengths exceeding 7 T to provide unparalleled imaging resolution [14]. Moreover, a 11.7 T MRI has recently been used in imaging human brains in France [15].

In current biological studies, SMFs are typically classified according to their intensity: weak (<1 mT), moderate (1 mT–1 T), high (1–20 T), and ultra-high (≥20 T) [16]. In addition to magnetic field intensity, SMFs also have various other parameters that can be classified into distinct categories. One such classification is based on their spatial distribution, where SMFs can be categorized as either homogeneous or inhomogeneous. In homogeneous fields, the magnetic field strength remains constant throughout the spatial domain, whereas in inhomogeneous fields, the strength varies across space [16]. Another critical parameter, often underexplored in current literature, is the direction of the SMF. The direction of the magnetic field can have significant implications for many biological effects, yet it has often been overlooked in many studies [17].

3. SMFs Are Generally Safe for Healthy Cells and Organisms

The use of high-field MRI and magnetic resonance spectroscopy (MRS) is heavily dependent on advancements in both magnetic and imaging technologies, as well as the assurance of biosafety. MRI systems operating at 1.5 T and 3.0 T are widely used in medical practice [18], while 9.4 T MRI machines have been evaluated in both rhesus monkeys and healthy human volunteers [19–21]. With growing public concern over health issues, there is increasing apprehension regarding the potential biological effects of SMFs in the range of 0.5–9.4 T, emitted by MRI machines in hospitals and clinical studies.

Current research suggests that SMFs up to 33 T pose no significant risk to healthy individuals (Table 1). At the cellular level, Zhang et al. demonstrated that exposure to a 1 T SMF did not significantly affect cell cycle progression or apoptosis, and a 10 T SMF did not impact the proliferation of Chinese hamster ovary (CHO) cells [22,23]. Similarly, for immortalized hamster cell lines and human primary cell lines, exposure to a 13 T SMF resulted in minimal effects on cell cycle distribution and cell viability [24]. Animal studies have further confirmed the safety of high SMFs in healthy subjects. For example, continuous exposure to SMFs ranging from 2.0 to 12.0 T for 4 weeks showed no adverse effects in healthy mice [25]. Moreover, exposure to fields of 3.5–23.0 T for 2 h or 7.0–33.0 T for 1 h did not trigger noticeable harmful effects on healthy mice [26,27]. However, exposure to a 13.5 T SMF with a gradient of 117.2 T/m led to increased spleen weight, though biochemical assays and hematological counts remained within normal limits [26]. In contrast, exposure to a 7 T SMF has been shown to offer potential benefits in antidepressant therapy without compromising safety [28]. Furthermore, in 2012, Qian et al. utilized a 21.1 T vertical bore magnet for high-resolution imaging of rodents, with no harmful effects reported [29]. In 2018, researchers in the National High Magnetic Field Laboratory in US have proposed that brain MRI and MRS techniques conducted at magnetic field strengths up to 20 T present no foreseeable safety concerns for humans [30].

More recently, Gu et al. found that although apoptosis and cell proliferation were unaffected by 11.2–33.0 T SMFs, exposure to 33.0 T for 1 h disrupted B cell differentiation and antibody production, while lower intensity SMFs (28.7, 17.8, and 11.2 T) did not produce such effects [31]. These findings suggest that while safety concerns may be associated with SMFs exceeding 30 T, SMFs below this threshold appear relatively safe for healthy mice.

Table 1. The safety study of SMFs on healthy cells and organisms.

Subject	SMF	Exposure Time	Biological Effects	Refs
Cell	1 T	2 d	No significant effect on cell cycle progression or apoptosis	[22]
	1.5 T and 7.05 T	24 h	Cell cycle analysis did not reveal differences between exposed cells and control cells	[32]
	10 T	4 d	No effect on CHO cell growth rate or cell cycle distribution	[23]
Mouse	0.15 T	6 months	It not only had good biosafety, but also improved the motor performance, mood, and function of ovarian, uterine, and intestinal microbiota abundance in adult female mice	[33]
	7 T	8 h	There are no adverse effects on normal and depressed mice, and SMF has the potential for antidepressant treatment on the basis of safety	[28]
	11.2 T and 11.8 T	1 h	Consistent with total splenic B cells, no clear differences were observed in IgM expression	[31]
	2–12 T	28 d	There were no significant adverse effects on healthy C57BL/6 mice	[25]
	16 T	1 h	There were no significant effects on body weight, organ coefficient or histomorphology of major organs in mice	[34]
	3.5–23 T	12 h	The mice are relatively safe and do not have serious effects on vital parameters or key organs	[35]
	7.0–33.0 T	1 h	Food and water intake, weight gain, blood counts, blood biochemistry and organ immunohistochemistry were examined and no serious long-term effects were found	[27]
	11.1–33 T	1 h	There were no adverse effects on healthy mice	[28]
	28.7 T and 33 T	1 h	Disturbance of B cell peripheral differentiation and antibody secretion	[31]
Human	9.4 T	30 min	Dizziness and lightheadedness are common and fairly clear acute side effects of high-field head movements, but there are no significant injuries	[19,20]
	11.7 T	5 min	Although a few volunteers involved transient dizziness when entering and exiting the magnet, it is possible to reach mesoscale resolutions within short acquisition times and with a high signal and contrast-to-noise ratio.	[15]

4. Influence of SMFs on Metabolic Diseases

The risk of metabolic diseases is primarily driven by dysfunction in the cells that regulate energy homeostasis, as well as by altered communication between various tissues and organs in which these cells reside. Many studies have shown that SMFs have a marked impact on mice with metabolic diseases, in contrast to their healthy counterparts (Figure 1). In this review, we synthesize experimental findings from three key areas where SMFs have demonstrated significant potential in the context of metabolic disorders: diabetes, fatty liver disease, and tumors. These areas offer considerable promise for the future integration of SMFs into medical and healthcare applications.

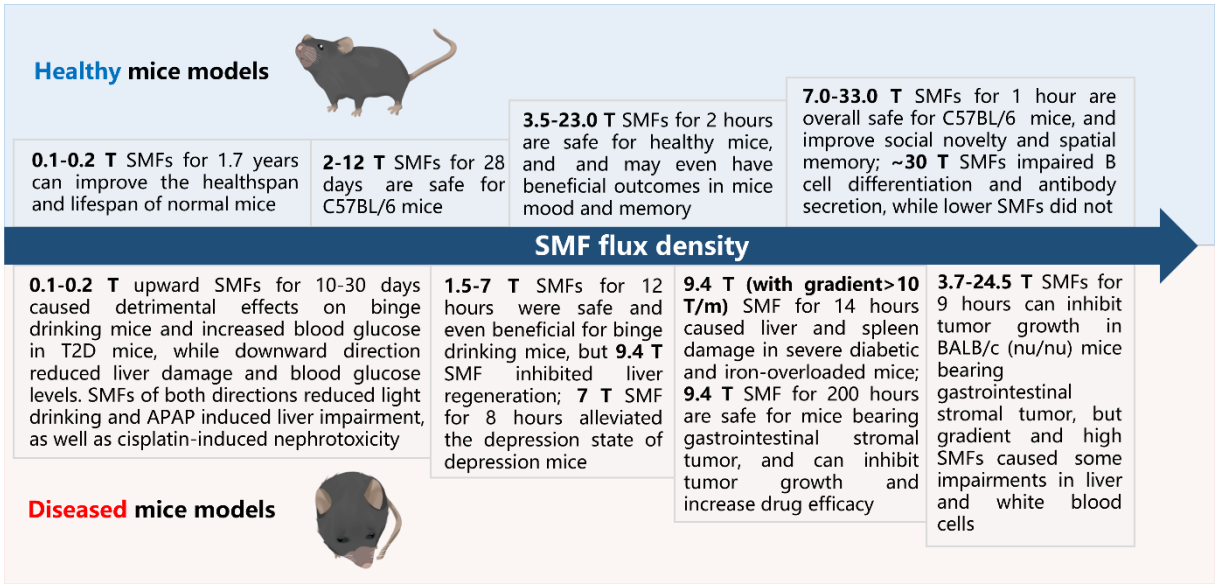


Figure 1. Significant differences in safety thresholds and magnetic field responses in mice with different disease states [6,25–28,31,35–43].

4.1. SMFs Induce Variable Effects in Different Metabolic Diseases

4.1.1. Weak to Moderate SMFs on Metabolic Diseases

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia, resulting from defects in insulin secretion and/or insulin action. It is primarily categorized into two forms: Type 1 diabetes (T1D) and T2D. Currently, T2D accounts for approximately 90–95% of all diabetes cases worldwide. T2D is a progressive metabolic condition that is marked by insulin resistance (IR) and impaired insulin secretion, often leading to systemic complications. These hallmarks serve as critical endpoints in research, enabling the assessment of disease progression and the evaluation of potential therapeutic interventions.

Diabetes

Multiple studies have investigated the effects of SMFs on diabetic models, particularly in mice, with mixed results [9,44,45]. Several reports suggest that weak to moderate SMFs could exert beneficial effects in alleviating various diabetic characteristics, such as hyperglycemia, insulin resistance, and associated metabolic dysfunctions. For instance, our group compared the effects of four different SMFs, varying in intensity, direction, and spatial distribution and found that a vertically downward near-homogenous ~100 mT SMF could significantly reduce the hyperglycemia, hepatic steatosis, and weight gain in T2D mice [6]. Similarly, Carter et al. conducted experiments with three different mouse models of diabetes and found that a combination of a 3 mT SMF and an electrostatic field improved blood glucose level, insulin sensitivity, and glucose tolerance in T2D mice [7]. In another study, exposure to SMFs ranging from 2.8 mT to 476.7 mT resulted in significant reductions in hyperglycemia in STZ-induced T1D mice [46]. Collectively, these findings highlight the potential therapeutic benefits of SMF exposure in the management of diabetes.

However, not all studies support the positive effects of SMFs on diabetes management. For example, a study of diabetic rats treated with a 180 mT SMF for 19 days reported no significant changes in blood glucose levels [47]. Similarly, rats treated with a 230 mT SMF for 7–20 days in STZ-induced diabetes showed no improvement in blood sugar control [48]. Additionally, Carter et al. found that after 25 days of treatment with a 3 mT SMF alone, glucose tolerance in diabetic mice worsened [7]. These contradictory results suggest that while weak to moderate SMFs may hold promise for improving certain diabetic features, their effects are not consistently beneficial, and in some cases, they may even have adverse effects.

Nevertheless, current findings indicate that although SMFs with varying parameters have differential effects on blood glucose regulation, they consistently exhibit positive effects on wound healing and diabetic osteoarthropathy (DOAP) in diabetic animal models [9,44,45]. For example, Feng et al. found that wound healing, liver lipid accumulation, and renal defects were significantly improved in genetically obese leptin receptor-deficient db/db diabetic mice by SMF treatment [49]. Moreover, Zhang et al. showed that 4 mT SMF exposure for

16 weeks inhibited the structural deterioration and mechanical strength reduction of trabecular and cortical bones in T1D rats [50].

Fatty Liver Disease

Fatty liver disease is primarily classified into two types: non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD). NAFLD is commonly associated with obesity and high-fat diets, leading to hepatic steatosis [51]. In contrast, ALD results from the toxic effects of alcohol metabolism on the liver, causing cellular damage and inflammation [52–56]. Both conditions share common features, including liver inflammation and steatosis, which contribute to disease progression [55,57].

Although the SMF effects on fatty liver disease are not entirely consistent across different studies, most of them suggest that weak to moderate SMFs can alleviate their progression and severities. For instance, in 2006, Park et al. found that exposure to a 0.3 T SMF could prevent alcohol-induced liver cell damage in rats [58]. Similarly, Song et al. observed that a vertically downward ~0.1 T SMF reduced lipid accumulation, liver inflammation, reactive oxygen species (ROS) levels, and oxidative stress in ALD mice, improving liver function [59]. However, the effects are different for SMFs with different directions, and for mice consuming different amounts of alcohol [59]. In a NAFLD model, Lv et al. demonstrated that exposure to a 0.6 T SMF reduced hepatic iron content and restored redox balance by modulating the MAPKs/Nrf2/HO-1 antioxidant pathway, thereby mitigating obesity-induced liver injury [60].

Tumor

Metabolic dysregulation, particularly increased aerobic glycolysis and anabolic pathways, as well as disturbances in iron metabolism, are important hallmarks of tumorigenesis. These metabolic alterations promote tumor development, metastasis, drug resistance, and the maintenance of cancer stem cells [61,62]. As a result, tumor cells display marked pathological and metabolic changes, leading to the emergence of diverse tumor cell lineages [63]. Although there are a few studies explored the relationship between SMFs and iron metabolism [64–66], how SMFs influence tumor cell metabolism is still unclear, which hinders our understanding for the underlying mechanisms of various reported effects of SMFs on tumor growth, metastasis, and angiogenesis.

At the cellular level, Song et al. reported that a 0.5 T SMF inhibited ovarian cancer cell migration, invasion, and stemness in a ROS-dependent manner [67]. Ghibelli et al. demonstrated that a 1 T SMF enhanced chemotherapy-induced apoptosis in human U937 monocytic tumor cells without affecting normal mononuclear leukocytes [68]. Furthermore, Zhang et al. also found that exposure to a 1 T SMF for 48 h reduced proliferation rates in six out of seven human tumor cell lines, particularly at higher cell densities [22]. However, some studies suggest that SMFs may promote cancer cell proliferation under certain conditions. For example, Fan et al. showed that a 0.15 T SMF stimulated the proliferation of 4T1 breast cancer cells, while inhibiting cell migration and telomerase activity, which minimized specific aspects of carcinogenesis [69]. Zhao et al. observed that exposure to 0.2–0.4 T SMFs increased ROS levels in osteosarcoma stem cells, stimulating their self-renewal ability [70]. These discrepancies may be attributed to differences in tumor cell types, treatment parameters, and experimental conditions.

In animal models, SMFs inhibit the growth of several types of cancer, including leukemia, colon cancer, and breast cancer [71,72]. For example, Strelczyk et al. treated melanoma-bearing mice with a 586 mT SMF and found that SMF exposure resulted in a significant delay in tumor growth, approximately 30% slower than controls, and a substantial reduction in functional vessel density, vessel diameters and red blood cell velocity in tumors compared to control tumors. [73]. Similarly, Gellrich et al. implanted LLC-1 tumor cells into mice and exposed them to a 587 mT SMF for 2 h after three days, resulting in a 46% reduction in tumor growth compared to the control group [74]. Notably, pre-exposure to a 400 mT SMF significantly enhanced the viability of NK92-MI cells by activating multiple MAPK signaling pathways and improved their capacity to eliminate K562 tumor cells [75]. However, Zhao et al. found that SMF treatment did not affect the tumor volume or tumor mass of K7M2 OSCs in tumor-bearing mice, nor pulmonary metastasis of K7M2 OSCs, but the SMF-treated K7M2 OSCs caused a preference of pulmonary metastasis in a mouse model, which suggested that SMF might induce the metastatic characteristic of OSCs [70].

4.1.2. Metabolic Diseases Have Different Safety Thresholds for High SMFs

Recent research indicates that high-gradient SMFs may have harmful effects on diabetic mice, with the severity of the damage being correlated with the progression of the disease [36]. Multiple studies suggest that uniform magnetic fields are generally safer than gradient fields in diabetic animal models. For example, Yu et al. reported that prolonged exposure to high-field SMFs (1.0–8.6 T) with gradients exceeding 10 T/m caused significant tissue damage in the spleen, liver, and kidneys of diabetic mice, particularly those with severe T1D. In contrast, exposure to 9.4 T SMFs with gradients below 10 T/m did not produce the same harmful effects [36]. Furthermore, the severity of diabetes appears to influence the sensitivity to SMF exposure. When healthy C57BL/6J mice were treated for 14 h with a ~9 T SMF at gradients of 10–20 T/m, no significant damage was observed. However, mild diabetic mice showed minor spleen damage, while severe diabetic mice exhibited significant splenic tissue damage [37]. These findings suggest that high SMFs may be harmful to diabetic mice, with the effects being contingent on both the field gradient and the disease severity.

Available data also suggest potential risks associated with high SMF exposure in mice with ALD. Wang et al. examined the effects of 12 h prolonged treatment of 1.5–9.4 T SMFs on both acute and chronic ALD mice, and revealed that exposure to SMFs ranging from 1.5 T to 7 T for 5–12 h was generally safe for both forms of ALD [38]. Notably, a 3 T SMF significantly reduced alcohol-induced oxidative stress and improved liver function in mice with both forms of ALD. However, exposure to a 9.4 T SMF inhibited DNA synthesis and liver regeneration in mice after high alcohol intake. The damage was more pronounced in mice with acute ALD than those with chronic ALD, highlighting the potential risks associated with high-field SMF exposure in the context of ALD [38]. These findings suggest that while exposure to some SMF conditions may have beneficial effects, prolonged high SMF exposure could exacerbate liver damage, particularly in acute liver injury.

Conversely, high SMFs exhibit much reduced harmful effects and more significant therapeutic benefits in cancer models. We found that exposure to a 9.4 T SMF for 88 h significantly inhibited the growth of A549 lung tumors in mice (approximately 44.7%) without causing obvious damage to key organs or blood cell counts [76]. Additionally, we also showed that a 9.4 T SMF treatment of gastrointestinal stromal tumors (GIST) tumor-bearing BALB/c (nu/nu) mice for 200 h could significantly reduce tumor growth (up to 62.88%) [39]. In fact, the 9.4 T SMF could also improve the anti-tumor effect of imatinib mesylate, reduce its toxicity and improve the mice mental health. However, for the same GIST tumor-bearing BALB/c (nu/nu) mice, SMFs at ~20 T treatment for 9 h reduced the tumor growth as well, but also caused some mild liver injury and abnormal white blood cell counts, although no serious harm was observed [40].

In summary, current research shows that different metabolic diseases have specific safety thresholds for SMF exposure. Weak to moderate SMFs can usually control metabolic disorders, depending upon the field strength, gradient, and uniformity, as well as the specific disease characteristics and severity. Conversely, high SMFs appear to have both beneficial and potentially harmful effects, depending on the pathological conditions being treated and the field gradient.

4.2. Factors Contributing to the Inconsistent Findings in the Literature on SMF Bioeffects in Metabolic Diseases

From the information above, it is obvious that SMFs of different flux density, or SMF intensity, would generate different effects on animals. However, it should be noted that other factors can also influence the bioeffects of SMF, especially in metabolic diseases.

4.2.1. SMF Direction

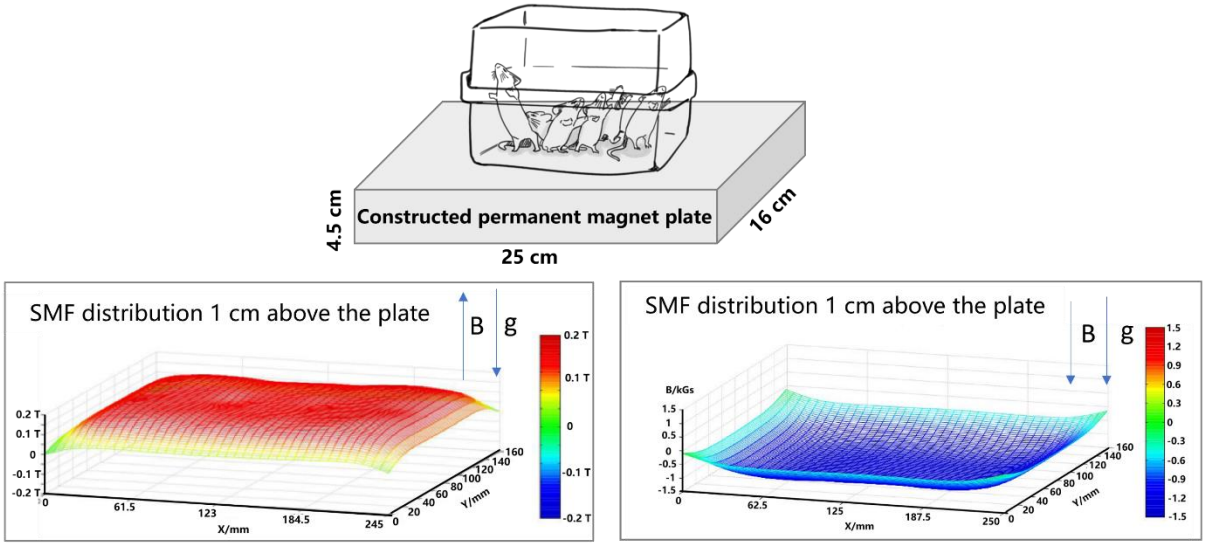
We first would like to emphasize SMF direction because it is one of the most frequently overlooked factors that contribute to the inconsistent experimental results about SMFs on metabolic diseases. To illustrate its importance, we summarize our data using exactly the same set of magnetic plates, including one with North (N) pole facing upward (vertically upward direction), and one with the South (S) pole facing upward (vertically downward direction) (Figure 2). They have the same magnetic flux density (B) of ~0.1 T, but with different directions. We also used unmagnetized plate as sham control. In our study, continuous exposure of healthy mice to SMFs for 1.7 years resulted in a significant improvement in both lifespan and healthspan [41]. However, it is very interesting that these SMFs generate distinct results on mice with different type of metabolic diseases.

In our diabetes studies, we revealed that the vertically downward SMF effectively reduced blood glucose levels in mice with T2D, alleviated liver damage, reduced lipid accumulation, and improved liver function, while also mitigating various diabetes-related complications [6]. In contrast, the vertically upward SMF even caused a slight increase in glucose levels. Additionally, the vertically downward SMF promoted the relative abundance of

beneficial gut microbiota in T2D mice, such as *Bacteroidetes* and *f_Muribaculaceae*, whereas the upward SMF did not exert a significant effect in the microbiome [6].

Variation was also observed in our studies on fatty liver disease. Although both upward and downward SMFs were found to reduce lipid accumulation, inflammation, and oxidative stress levels in the livers of mice with lighter alcohol consumption, the vertically downward SMF produced more pronounced effects [59]. Interestingly, the upward SMF inhibited DNA synthesis and liver cell regeneration in "heavy drinking" mice, negatively impacting their survival. Conversely, the downward SMF extended their lifespan [59]. Moreover, in acute liver injury models induced by high doses of acetaminophen (APAP), both upward and downward SMFs reduced mortality induced by high APAP doses, while the downward SMF exhibited a more pronounced protective effect [42].

The directional effects of SMFs were also found to be particularly significant in tumor models. Notably, vertically upward and downward SMFs at ~0.1 T reduced cisplatin-induced nephrotoxicity, with the downward SMF being more effective [43]. However, at a higher flux density of 9.4 T, tumor exposure to a vertical upward magnetic field appeared more beneficial than the downward direction. For instance, we observed that a 9.4 T SMF applied in the upward direction for 88 h significantly inhibited tumor growth in A549 tumor-bearing mice, with a tumor growth inhibition rate of approximately 41%. In contrast, no significant tumor inhibition was observed with 9.4 T SMF of downward direction [76]. A detailed discussion of the underlying mechanisms will be presented in a subsequent section of this review.



Mice	Duration	Results
Healthy C57BL/6	1.7 years	Live longer and healthier
HFD+STZ induced T2D C57BL/6	12 weeks	Increase blood glucose
Binge alcohol drinking BALB/c	6 weeks	Increase lethality
Low dose alcohol drinking BALB/c	3 weeks	Reduce liver damage
High dose APAP injected C57BL/6	2-33 days	Reduce liver damage
High dose cisplatin injected C57BL/6	2 days	Increase survival

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Figure 2. The impact of ~0.1 T SMF in different directions on various metabolic diseases [6,41–43,59]. (**Left**) SMF with vertically upward direction, opposite to the gravity (g) direction, provided by a magnetic plate with the N pole facing up. (**Right**) SMF with vertically downward direction, the same as the gravity (g) direction, provided by a magnetic plate with the S pole facing up. The whole mice cages were placed on the top of the magnetic plates.

4.2.2. Influence of Other Parameters on the Magnetic Effects in Metabolic Diseases

In addition to the intensity and direction of SMFs, other treatment parameters, such as SMF gradient, exposure time and pattern, all play indispensable roles in determining their effects on metabolic diseases [16]. In general, weak to moderate SMFs with low gradient are safe for healthy mice and may offer therapeutic benefits for managing some moderate metabolic disorders. Conversely, SMFs with high-gradient and high intensity may induce harmful effects in metabolic disease models, especially with severe conditions.

5. Mechanisms of SMF Effects on Metabolic Diseases

As outlined above, the biological effects of SMFs on metabolic diseases are influenced by multiple factors, including SMF treatment parameters (such as exposure duration, frequency, and interval), SMF characteristics (such as field intensity, gradient, direction, and spatial distribution), as well as the physiological and pathological conditions of the animal model. Although the underlying mechanisms driving these differential effects are not yet fully understood, we now have a preliminary framework for understanding how different SMFs can impact various aspects of living organisms (Figure 3).

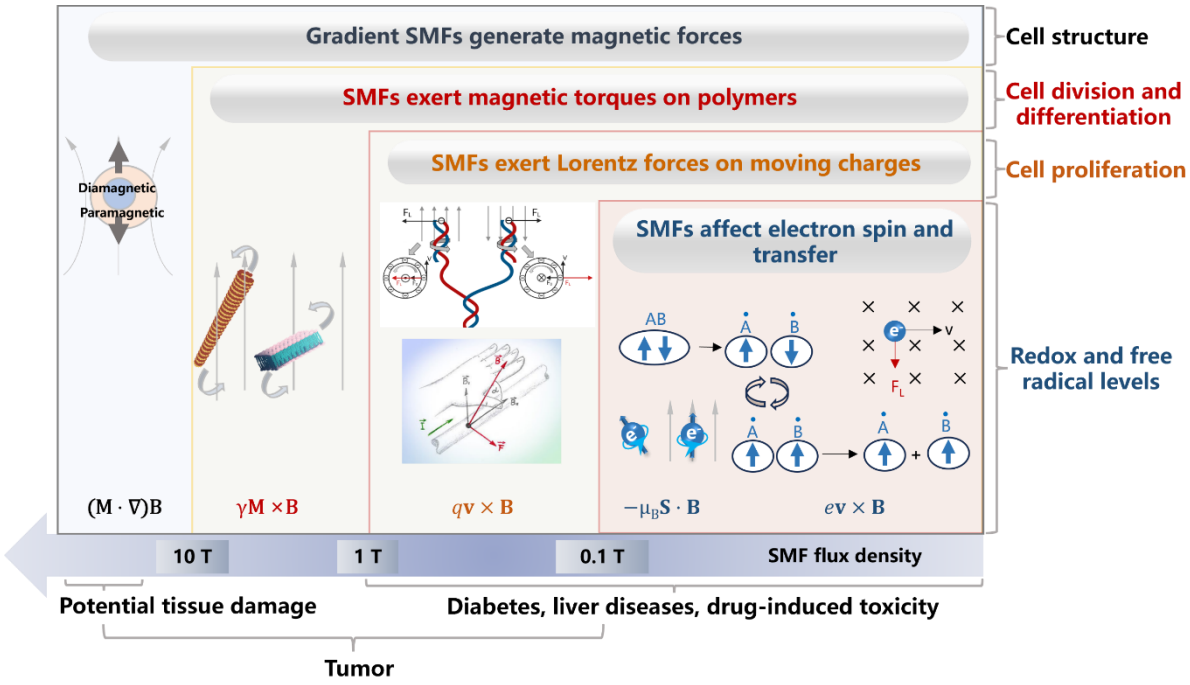

Figure 3. A preliminary framework of the mechanisms of SMF bioeffects.

5.1. SMFs Affect Electron Spin and Transfer to Regulate Redox and Free Radical Levels

SMFs can modulate electron states and influence unpaired electrons within free radicals, providing a theoretical basis for the regulation of ROS by SMFs in cells [77]. Free radicals, key constituents of ROS, include atoms, molecules, or compounds that possess high instability due to their atomic or molecular structure, specifically the distribution of electrons. This instability confers a high degree of reactivity upon free radicals, prompting them to seek pairing with other molecules, atoms, or individual electrons to form stable compounds. It is proposed that the transitions between singlet and triplet states, as well as the recombination of radical pairs, can be modulated by magnetic fields [77–80], thus affecting intracellular ROS levels. In both diabetes and fatty liver disease, exposure to near-homogenous ~0.1 T SMFs reduced ROS in the liver, mitigating disease-related damage [6,59]. In fact, this SMF can directly reduce free radical production in H_2O_2 solution [59]. Of note, the impact of SMFs on free radical levels in living cells appears to be dependent on both the intensity and frequency of the applied field, as well as the specific cell type [81].

Since the key process of the redox reactions is electron transfer, they can also be affected by SMFs. In fact, there are many studies have shown that SMFs can be used to increase electron transfer and boost electrochemistry and electrocatalysis [82–86]. Moreover, mitochondria, the essential organelles in cells responsible for generating energy through cellular respiration, involves the transfer of electrons through the mitochondrial electron transport chain (ETC). From our point of view, mitochondria, iron metabolism and Fenton reactions are all important targets

for SMF-induced changes in metabolic diseases. However, to the best of our knowledge, there is still a lack of direct evidence and experimental studies investigating the effects of SMFs on electron transfer in metabolic diseases, which is an ongoing project of our group.

5.2. SMFs Exert Lorentz Forces on Moving Charges to Affect Cellular Processes Such as Cell Proliferation

As the intensity of the applied SMF increases, the Lorentz forces acting on charged molecules proportionally increases, which alter their movement. One obvious example is the SMF-induced nystagmus and vertigo through vestibular system, which has ionic currents naturally occurring in the lymphatic fluid inside the labyrinth. It has been shown that SMFs generate Lorentz forces that push against the apex of the semicircular canals, resulting in nystagmus [87]. Another example is DNA synthesis. Given that DNA is negatively charged and undergoes rapid rotation during replication, externally applied SMFs can affect DNA movement through the Lorentz force [88], ultimately impacting DNA synthesis, tumor cell proliferation, and liver regeneration. Given that the direction of Lorentz forces depends on the charge, the moving direction and the SMF direction, SMFs of opposite directions will generate opposite Lorentz forces on the same charged moving molecule. Notably, the vertically upward SMFs, which is opposite to the gravity direction, tend to inhibit DNA synthesis, while the vertically downward SMFs have differential effects, depending on the SMF intensity and cell types [42,59,76,88]. Moreover, besides DNA, the moving charges in ion channels are also targets of SMFs, which is one of the current focuses of our group.

5.3. SMFs Exert Magnetic Torques on Polymers to Affect Cellular Processes Such as Cell Division and Differentiation

At higher field intensities, particularly those exceeding 1 T, SMFs will generate more effects, especially on structures that have a strong structure anisotropy, such as cell membrane, microtubules and actin filaments. For example, Valiron et al. demonstrated that ultra-high SMFs in the 7–17 T range can affect the microtubule and actin cytoskeleton in certain cell types [89]. In our own studies, we found that exposure to a 1 T SMF for 7 days caused spindle abnormalities in human cervical cancer cells, leading to division arrest [90]. Moreover, 27 T ultra-high SMF exposure for 4 h induced mitotic spindle abnormalities in human nasopharyngeal carcinoma cells, reducing the number of viable cells by approximately 50% after 3 days of treatment [91]. It should be mentioned that SMFs of moderate intensity ($\leq$1 T) for 4 h did not exhibit such effects. Since the mitotic spindle, primarily composed of microtubules, plays a central role in the process of cell division, it is not surprising that high SMFs can affect the orientation of the mitotic spindle and impede cell division. Moreover, there are multiple lines of evidence indicating that high SMFs can align cells or biomolecule polymers, including red blood cells, sperm, collagen, DNA, etc. [92].

5.4. Gradient SMFs Generate Magnetic Forces to Affect Cell and Tissue Structures

In high-intensity and high-gradient SMFs, tissues and cells within the body will experience varying magnetic forces due to their subtle different magnetic susceptibility. We also found that metabolic diseases can alter the magnetic susceptibility of specific tissues [37], thereby modifying their magnetic properties. This change in biomagnetic characteristics may be a primary factor mediating the detrimental effects of high-gradient SMFs on metabolic disease models. Studies have shown that in healthy mice, the magnetic susceptibility of organs is primarily attributed to diamagnetic water, resulting in weak diamagnetism throughout the organs [93]. Consequently, exposure to magnetic fields in healthy animals typically does not cause significant harmful effects. However, in severely diabetic mice, paramagnetic iron deposits in the spleen red pulp alter the spleen's magnetic properties. Since the magnetic force is proportional to the magnetic flux density (B), the gradient of the magnetic field (∇B), and the magnetic susceptibility of tissues, diamagnetic and paramagnetic objects experience opposite forces in a gradient field [37,94]. The uneven distribution of magnetic susceptibility within the cell or tissue leads to differential magnetic forces when exposed to high-intensity and high-gradient magnetic fields, which can result in cell function abnormality and tissue injury.

6. Conclusion and Prospects

In summary, although existing studies on the magnetic effects in metabolic diseases often encounter issues with reproducibility, current experimental results in the literature suggest that weak to moderate SMFs may offer potential therapeutic benefits for certain metabolic diseases, while high-intensity and high-gradient SMFs may pose potential health risks. It is clear that the effectiveness and safety thresholds for SMF exposure vary significantly across different metabolic conditions, influenced by factors such as field intensity, direction, disease

type and severity. In addition, although current findings already provide some valuable insights for future human studies, the inherent complexity of biomagnetic systems limits the ability to derive precise and universally applicable patterns or conclusions regarding the exact rules for magnetic field effects on metabolic diseases. Currently, how exactly different physiological and pathological states contribute to differential SMF bioeffects still remain incompletely understood. Future research should aim to explore how metabolic diseases and other severe pathological conditions can alter the magnetic properties of organisms, which not only influences SMF bioeffects, but also provides a foundation for advancing the development of novel diagnostic and therapeutic approaches based on biomagnetism.

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