Chapter 10
Effects of Static Magnetic Fields on Diabetes and Its Complications

Chuanlin Feng, Biao Yu, and Xin Zhang

Abstract Diabetes, a metabolic chronic disease characterized by hyperglycemia, has dire consequences for health and well-being if left uncontrolled. In recent years, there are some studies about the effects of static magnetic fields (SMFs) on diabetes and its complications, but the reported effects are highly inconsistent, especially for glycemia levels. The aim of this chapter is to compare and analyze reported effects of multiple parameter SMFs on glycemia and insulin levels, as well as diabetic complications. It is interesting that although the reported effects of SMFs on glycemia and insulin levels are variable due to the differences in SMF parameters and experimental subjects, SMFs have consistently shown beneficial effects on diabetic complications including wound healing. Mechanistic studies indicate that SMFs may play an important role in insulin secretion by affecting membrane proteins, hormone levels, and reactive oxygen species. This not only contributes to a better understanding of SMF effects on diabetes and its complications, but also lays the foundation for more systematic and in-depth studies to develop potential applications of SMFs in the clinical setting of diabetes in the future.

Keywords Magnetic field (MF) · Static magnetic field (SMF) · Glycemia · Insulin · Diabetes · Diabetic complications · Mechanisms

10.1 Introduction

Diabetes mellitus is a serious chronic condition with hyperglycemia, mostly because the body cannot generate enough insulin or cannot efficiently utilize insulin. There are two main types of diabetes, including type 1 diabetes mellitus (T1D, or T1DM) and type 2 diabetes mellitus (T2D, or T2DM). But there are also some specific forms

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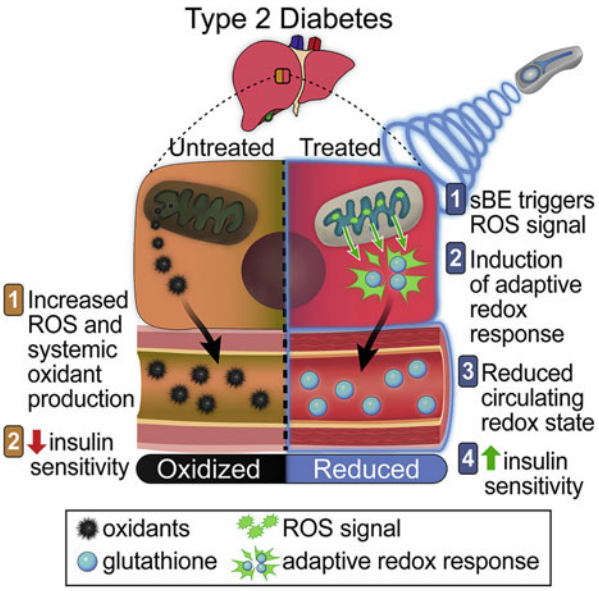

Fig. 10.1 A combined static magnetic field and static electric field can alleviate T2D. [Reprinted from reference with permission (Carter et al. 2020).]

of diabetes mellitus, for example, diabetes that occur during pregnancy, or mediated by drugs or chemicals, viral infections, etc. (Forbes and Cooper 2013; Magliano et al. 2021). Among the various reasons for triggering diabetes, the main causes include autoimmune destruction of pancreatic islet cells, insulin resistance, and insufficient insulin secretion (American Diabetes Association 2010). Besides hyperglycemia, diabetes can also cause a series of complications, including dysfunctions in the kidney, retina, cardiovascular system, neurons, and liver, which are the major causes of morbidity and mortality in diabetic patients (Morrish et al. 2001; Demir et al. 2021).

In recent years, there are multiple studies that have reported the effects of magnetic fields on diabetes and its complications. For example, Carter et al. performed multiple mice experiments to demonstrate that a combined static magnetic field (SMF) and static electric field can effectively improve glycemia, insulin resistance, and glucose intolerance in T2D (Carter et al. 2020) (Fig. 10.1). Our group compared four types of moderate SMFs, with different SMF flux, directions, and distributions, and found that a ~100 mT vertically downward direction SMF could effectively alleviate the development of hyperglycemia, fatty liver, and weight gain in T2D (Yu et al. 2021) (Fig. 10.2). Both of these two studies have showed beneficial effects on T2D and both of them have pointed out that the oxidative stress regulation plays an essential role. In this chapter, we will focus on the effects and mechanisms of various types of SMF treatments on glycemia, diabetes and its complications.

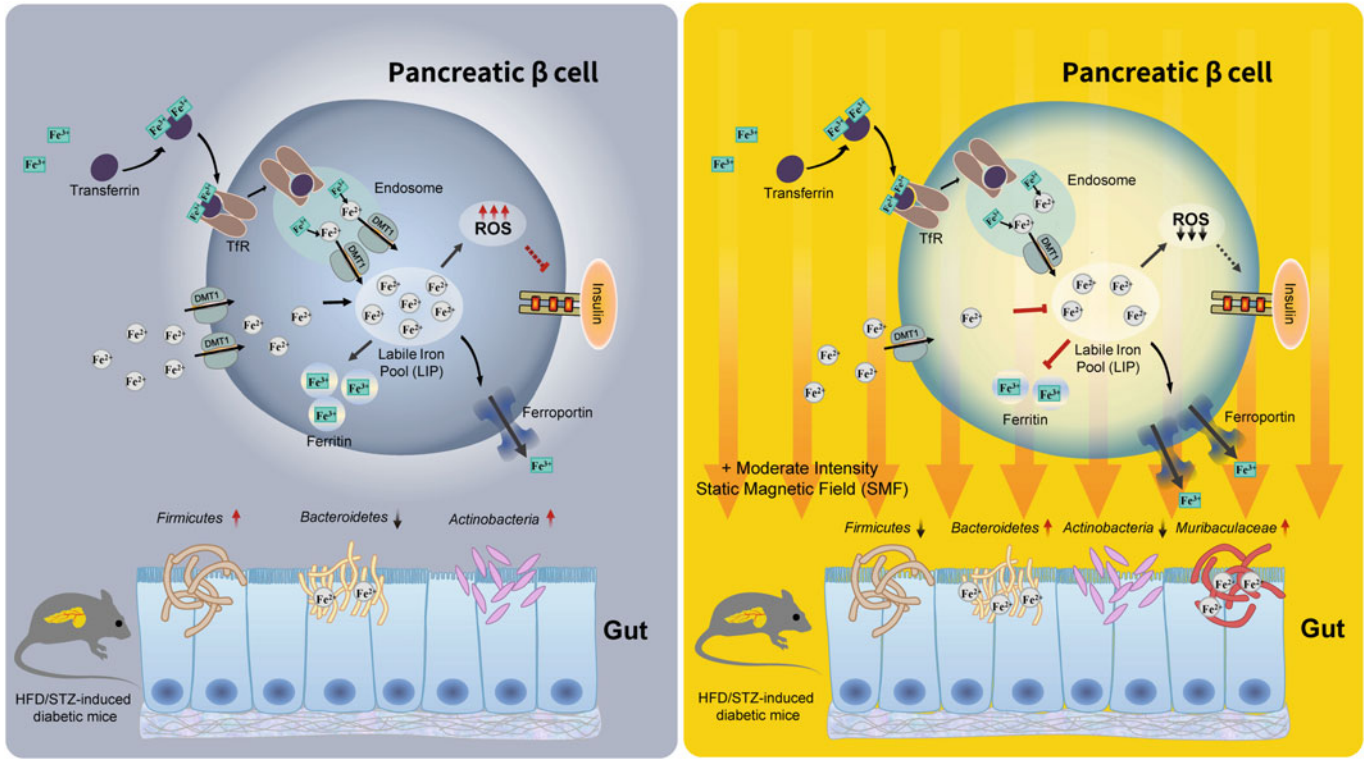

Fig. 10.2 A ~100 mT downward direction static magnetic field improves iron metabolism and prevents high-fat diet/streptozotocin-induced T2D. [Reprinted from reference with permission (Yu et al. 2021).]

10.2 Effects of Static Magnetic Fields on Glycemia Levels in Diabetic Animals

Currently, the effects of various SMFs on glycemia, the key indicator for diabetes diagnosis, in diabetic model animals are still inconsistent (Table 10.1), which is largely due to the SMF parameter differences in different experiments. Some studies have reported that SMF can raise glycemia levels. For example, Carter et al. reported that 3 mT horizontal SMF exposure for 7 h/day for consecutive 25 days significantly increased glycemia (Carter et al. 2020). Conversely, studies have also reported that SMF can decreased glycemia levels. Li et al. reported that alternating pole SMFs (400 and 600 mT) exposure for 24 h can also induce glycemia reduction (Li et al. 2020). In addition, there are also studies that found no effect of SMF on glycemia. For example, our group found no statistically changes in glycemia levels in db/db mice after exposure to ~15 mT inhomogeneous SMF (Feng et al. 2022). Zhang et al. used a 4 mT equipment to treat with diabetic rats for 16 weeks and did not observe significant changes in glycemia levels either (Zhang et al. 2018). We found that T2D mice treated with ~100 mT upward direction SMF for consecutive 12 weeks increased the glycemia level, while the downward SMF decreased glycemia (Yu et al. 2021). These demonstrate that SMF parameter, especially SMF direction, is critical for the SMF effects on glycemia.

10.3 Effects of Static Magnetic Fields on Insulin Levels in Diabetic Animals

Generally speaking, increased insulin levels usually correspond to the decreased glycemia. However, it is not always the case because insulin resistance is another important feature of diabetes, which results in reduced sensitivity of the body to insulin. As far as we know, there are only three studies that have reported the effects of SMFs on insulin levels in diabetic mice, and their results are also variable (Table 10.2). However, Carter et al. found that although the combined static magnetic and electric fields decreased insulin secretion, they still can decrease glycemia by increasing the insulin sensitivity in mice (Carter et al. 2020). Therefore, people are recommended to also measure the insulin sensitivity in their studies to get a more comprehensive understanding of how SMFs affect the glucose metabolism. In our study, we found that the ~100 mT downward direction SMF not only increased the insulin levels, but also improved the insulin sensitivity in high-fat diet (HFD)/streptozotocin (STZ)-induced T2D mice (Yu et al. 2021).

Table 10.1 Effects of static magnetic fields on glycemia levels in diabetic animals

Species	Induction modality	SMF parameters	Exposure time	Glycemia levels	Other effects	References
C57BL/6J mice	HFD induction for 4–8 weeks	3 mT horizontal direction	7 h/day, 25 days	Increased	Elevated glycemia and worsened glucose tolerance	Carter et al. (2020)
	HFD induction for 6 weeks, then intraperitoneal injection of 45 mg kg^{-1} STZ for 3 consecutive days	~100 mT upward direction	24 h/day, 12 weeks		Significantly reduced glucose clearance, exacerbates hepatocyte steatosis, increases iron storage	Yu et al. (2021)
CD1 mice	Intraperitoneal injection of STZ at a dose of 100, 150, 200 mg kg^{-1}	2.8–476.7 mT	30 min/day, 6 weeks	Decreased	N/A	László et al. (2011)
C57BL/6J mice	HFD induction for 6 weeks, then intraperitoneal injection of 45 mg kg^{-1} STZ for 3 consecutive days	~100 mT downward direction	24 h/day, 12 weeks		Reduced hyperglycemia, body weight, tissue damage in T2D mice; regulated iron metabolism, improved oxidative stress and viability of pancreatic islet cells	Yu et al. (2021)
ICR mice	HFD induction for 2 weeks, then intraperitoneal injection of 80 mg kg^{-1} STZ for 3 consecutive days	400 mT, 600 mT, alternating pole	24 h/day, 60 days		Reduced glycemia, improved glucose tolerance, improved lipid metabolism, increased insulin secretion	Li et al. (2020)
Sprague-Dawley rats	Intravenous injection of STZ at a dose of 50 mg kg^{-1}	4 mT	2 h/day, 16 weeks	No change	N/A	Zhang et al. (2018)
db/db mice	Spontaneous type	~15 mT	24 h/day, 10 weeks			Feng et al. (2022)
Sprague-Dawley rats	Intraperitoneal injection of STZ at a dose of 60 mg kg^{-1}	180 mT	24 h/day, 5–19 days			Jing et al. (2010)
ICR mice	HFD induction for 2 weeks, then intraperitoneal injection of 80 mg kg^{-1} STZ for 3 consecutive days	200 mT	24 h/day, 60 days			Li et al. (2020)

(continued)

Table 10.1 (continued)

Species	Induction modality	SMF parameters	Exposure time	Glycemia levels	Other effects	References
Wistar rats	Subcutaneous injection of STZ at a dose of 65 mg kg^{-1}	230 mT	24 h/day, 7–21 days			Zhao et al. (2017)
C57BL/6J mice	HFD induction for 6 weeks, then intraperitoneal injection of 45 mg kg^{-1} STZ for 3 consecutive days	400 mT, 600 mT, alternating pole	24 h/day, 12 weeks			Yu et al. (2021)

Table 10.2 Effects of static magnetic fields on insulin levels in diabetic animals

Species	Induction modality	SMFs parameters	Exposure time	Insulin levels	Other effects	References
C57BL/6J mice	HFD induction for 6 weeks, then intraperitoneal injection of 45 mg kg^{-1} STZ for 3 consecutive days	~100 mT downward direction	24 h/day, 12 weeks	Increased	Downward SMF improved pancreatic function by regulating iron metabolism, reactive oxygen species (ROS) production, and gut microbiota, increased the area of the pancreatic islets and improved the insulin sensitivity	Yu et al. (2021)
ICR mice	HFD induction for 2 weeks, then intraperitoneal injection of 80 mg kg^{-1} STZ for 3 consecutive days	200 mT, 600 mT, alternating pole	24 h/day, 60 days		600 mT alternating pole SMF slightly increased the number of cells in the islets	Li et al. (2020)
Sprague-Dawley rats	Intravenous injection of STZ at a dose of 50 mg kg^{-1}	4 mT	2 h/day, 16 weeks	No change	N/A	Zhang et al. (2018)
C57BL/6J mice	HFD induction for 6 weeks, then intraperitoneal injection of 45 mg kg^{-1} STZ for 3 consecutive days	~100 mT upward direction	24 h/day, 12 weeks		Upward SMF decreased the insulin sensitivity	Yu et al. (2021)
ICR mice	HFD induction for 2 weeks, then intraperitoneal injection of 80 mg kg^{-1} STZ for 3 consecutive days	400 mT alternating pole	24 h/day, 60 days		400 mT alternating pole SMF slightly increased the number of cells in the islets	Li et al. (2020)

10.4 Effects of Static Magnetic Fields on Diabetic Complications

The hyperglycemia of diabetes produces glucotoxicity that cause damage to the macrovasculature system (cardiovascular disease), microvasculature system (diabetic nephropathy, diabetic retinopathy, and neuropathy), and other tissues (diabetic bone, diabetic foot, and diabetic encephalopathy), resulting in various complications (Ceriello 2005; Cole and Florez 2020).

Diabetes significantly impairs bone formation, reduces the mechanical strength of bone, and ultimately leads to osteoporosis (Hofbauer et al. 2022). It also accelerates the degeneration of skeletal structures (Rabe et al. 2021), makes diabetic patients more prone to fractures (Janghorbani et al. 2007; Wang et al. 2019) and difficult to heal after fractures (Retzepi and Donos 2010), which make the mortality rate due to fractures significantly higher than that of the non-diabetic population (Gulcelik et al. 2011). In 2018, Zhang et al. showed that a 4 mT SMF treatment (2 h/day, 16 weeks) can improve bone stiffness, increase the expression of osteogenesis-related genes, and improve symptoms associated with diabetic osteoarthropathy (Zhang et al. 2018). Although it is the only report so far that has investigated on the SMF effects on diabetes osteoarthropathy (Zhang et al. 2018) as far as we know, there are actually a large number of studies demonstrated that SMFs can exhibit positive effects on the skeletal system of non-diabetic animals, which has been reviewed (Zhang et al. 2014) and discussed in the Chap. 11 of this book. Moreover, our group found that a ~100 mT downward direction SMF increased the number of trabecular osteoblasts in the tibia of T1D mice, but not in 0.5 T upward SMF (unpublished data).

Moreover, it should be noted that at least 50% of diabetic patients suffer from diabetic neuropathy, a set of clinical syndromes caused by damage to the peripheral and autonomic nervous systems, which causes allodynia, spontaneous pain, burning, and numbness (Feldman et al. 2019). Similar to the above-mentioned effect of SMFs on bone, there are also many studies of SMFs on nervous system in non-diabetic animals, which will be discussed in Chap. 13 of this book. However, there are only two studies so far that have investigated the effects of SMFs on diabetic neuropathy and the results are still inconclusive. László et al. examined the STZ-induced CD1 mice treated with 2.8–476.7 mT inhomogeneous SMF for 0.5 h/day for 6 weeks and found no significant effect (László et al. 2011). However, Weintraub et al. found that shoe insole of 45 mT alternating pole SMF (24 h/day, 4 months) can play a mitigating role in patient feet with symptoms associated with diabetic neuropathy (Weintraub et al. 2003).

Lastly, it is well known that one of the most prevalent complications in diabetic patients is diabetic wounds (Bowling et al. 2015), which are usually hard to heal and can lead to infection, amputation, and even death (Falanga 2005; Lavery et al. 2010; Lipsky et al. 2012). It is interesting that although various SMFs have inconsistent effects on glycemia, insulin levels, and diabetic neuropathy, all four reported studies of SMFs on wound healing in diabetic mice we got from the literature showed very consistently positive effects (Table 10.3). In fact, in 2021, Lv et al. have reviewed

Table 10.3 Static magnetic fields accelerate diabetic wound healing in all four reported studies

Species	Induction modality	SMFs parameters	Exposure time	Specific results	References
db/db mice	Spontaneous type	~15 mT	24 h/day, 22 days	Facilitated wound closure and re-epithelialization, reduced necrotic areas of wound tissue, increased collagen fibers, improved cell viability and migration, reduced cell death, significantly reduced nuclear factor erythroid 2-related factor 2 levels, and decreased intracellular oxidative stress	Feng et al. (2022)
Sprague-Dawley rats	Intraperitoneal injection of STZ at a dose of 60 mg kg^{-1}	180 mT	24 h/day, 5–19 days	Inflammatory cell counts and necrosis levels were significantly reduced. Healing rate was significantly increased, and the total healing time was shortened. Collagen deposition and wound tensile strength were substantially increased	Jing et al. (2010)
Wistar rats	Subcutaneous injection of STZ at a dose of 65 mg kg^{-1}	230 mT	24 h/day, 7–21 days	Wound area reduction rate was significantly accelerated. Total wound healing time was reduced. Wound tissue strength and stress levels were significantly enhanced	Zhao et al. (2017)
db/db mice	Spontaneous type	600 mT	24 h/day, 14 days	Accelerated wound healing, promoted re-epithelialization, revascularization, and inflammation regression, and upregulated anti-inflammatory gene expression	Shang et al. (2019)

about the effects of multiple types of magnetic fields, including time-varying magnetic fields, on diabetic wounds, which show that all types of magnetic fields have positive effects in promoting diabetic wound healing, according to the literature (Lv et al. 2021). This is interesting and promising, but the reasons for this phenomenon are varied and still unclear.

10.5 Effects of Static Magnetic Fields on Glycemia and Insulin Levels in Cells and Non-Diabetic Animals

Besides the studies of SMFs on diabetic animals, there are actually quite a few studies performed on non-diabetic animals (Table 10.4). Similar to that of diabetic animals, the results in non-diabetic animals are also inconsistent. However, it is interesting that there are no studies reporting decreased glycemia levels in non-diabetic animals so far. Gorczynska et al. found that blood glucose in Wistar rats can be elevated by 1 mT and 10 mT SMFs (Gorczynska and Wegrzynowicz 1991). Meanwhile, several works by Lahbib et al. also found that 128 mT SMF increased glycemia levels in Wistar rats (Lahbib et al. 2010, 2015a, b). In addition, some studies have also shown no effect of SMF on glycemia levels. Currently, we cannot make an accurate conclusion or explanation because of the differences in mice strains, SMF parameters, and SMF treatment methods.

Moreover, insulin levels were also investigated in many studies in cells and non-diabetic mice (Table 10.5). We found that treatment of INS-1 cells with 400 mT SMF for more than 6 h can increase insulin expression and secretion (Mao et al. 2015, 2017), and the exposure of INS-1 cells with 6 T SMF for 1 h can also increase insulin secretion (Sakurai et al. 2009). Interestingly, studying the effects of SMFs on islet cells isolated from Sprague-Dawley rats, Hayek et al. found that the SMF increases insulin levels in a magnetic flux density-dependent manner at magnetic flux density of 0.1–1 mT and lower initial glucose concentrations (5.4 mmol/L) (Hayek et al. 1984). In contrast, these effects were not significant at higher (16.7 mmol/L) initial glucose concentration conditions (Hayek et al. 1984). From the above results, we speculate that the influence of SMFs on insulin is related to the magnetic flux density, exposure time, and the initial glucose level.

10.6 Analysis of Inconsistent Effects of Static Magnetic Fields on Glycemia or Insulin

It is obvious that SMFs have generated very variable effects on most aspects of diabetes and complications, except for the diabetic wound healing. We think there are multiple factors that contribute to these inconsistencies, which are discussed below.

First of all, the major factor is the SMF parameters, including distributions (direction and gradient, etc.) and flux densities generated by the different devices (Fig. 10.3), especially the SMF direction. Our group has previously reported on the SMF direction-induced differential bioeffects (Tian et al. 2018; Yang et al. 2020, 2021) and has also systematically summarized them in Chap. 2 of this book. Moreover, we have side-by-side compared four different SMF settings and different exposure times on HFD/STZ-induced T2D mice. We found that different magnetic flux densities, distributions, directions, and treatment time could produce totally

Table 10.4 Effects of static magnetic fields on glycemia levels in non-diabetic animals

Species	SMF parameters	Exposure time	Glycemia levels	Other effects	References
Wistar rats	1 mT, 10 mT	1 h/day, 10 days	Increased	Elevated levels of growth hormone, thyrotropin, thyroid hormone, cortisol, and glucagon. Decreased insulin levels	Gorczynska and Wegrzynowicz (1991)
	128 mT upward direction	1 h/day, 15 days		Elevated glycemia, lactated glycerol, cholesterol, and phospholipids. Decreased plasma insulin levels. Significantly decreased glycogen levels in quadriceps and liver tissue	Elferchichi et al. (2010)
				Decreased body weight, liver weight, lactate, cholesterol, phospholipids, serum insulin, and triglyceride levels	Elferchichi et al. (2011)
		1 h/day, 5 and/or 15 days		Significantly elevated plasma levels of glycerol, cholesterol, phospholipids, serum insulin, and lactate. Decreased liver glycogen levels	Lahbib et al. (2010)
		1 h/day, 5 days		Reduced islet area and lack of glucose transporters 2 (GLUT2) expression in the outer membrane of islet cells	Lahbib et al. (2015a)
				Decreased plasma insulin levels	Lahbib et al. (2015b)
		1 h/day, 13 days		Increased hematocrit and hemoglobin concentration. Increased aspartate aminotransferase and lactate dehydrogenase activity. Decreased plasma insulin levels	Chater et al. (2006)
		1 h/day, 10 days		Elevated platelet and hemoglobin levels. Increased aspartate aminotransferase and lactate dehydrogenase activity	Sihem et al. (2006)
BALB/c mice	– $2.9 \sim +2.9 \times 10^{-6}$ T	24 h/day, 30 days	No change	N/A	Hashish et al. (2008)
	50 mT	10 h/day, 25 days			Abbasi et al. (2007)

Table 10.5 Effects of static magnetic fields on insulin levels in cells and non-diabetic animals

Species	SMF parameters	Exposure time	Insulin level	Other effects	References
INS-1 cells	400 mT	12–72 h	Increased	Upregulates the expression of pancreatic-specific transcriptional factors and vesicular secretory proteins. Enhances insulin gene promoter activity and enhances insulin gene expression	Mao et al. (2017)
	400 mT	6–18 h		Increased insulin gene expression	Mao et al. (2015)
	6 T horizontal direction	1 h			Sakurai et al. (2009)
Wistar rats	1 mT, 10 mT	1 h/day, 10 days	Decreased	Increased levels of glucagon, growth hormone, thyrotropin, thyroxine, cortisol	Gorczynska and Wegrzynowicz (1991)
	128 mT upward direction	1 h/day, 13 days		Elevated platelet and hemoglobin levels. Increased aspartate aminotransferase and lactate dehydrogenase activity	Chater et al. (2006)
		1 h/day, 15 days		Elevated glycemia, lactated glycerol, cholesterol, and phospholipids. Decreased plasma insulin levels. Significantly decreased glycogen levels in quadriceps and liver tissue	Elferchichi et al. (2010)
				Decreased body weight, liver weight, lactate, cholesterol, phospholipids, and triglyceride levels	Elferchichi et al. (2011)
				Significantly elevated plasma	Lahbib et al. (2010)

(continued)

Table 10.5 (continued)

Species	SMF parameters	Exposure time	Insulin level	Other effects	References
		1 h/day, 5 and/or 15 days		levels of glycerol, cholesterol, phospholipids, and lactate. Decreased liver glycogen levels	
		1 h/day, 5 days		Reduced islet area and lack of GLUT2 expression in the outer membrane of islet cells	Lahbib et al. (2015a)
				N/A	Lahbib et al. (2015b)
Isolated pancreatic islet cells from Sprague-Dawley pregnant rats	0.1–1 mT	48 h	Insulin levels depend on initial glucose concentration and magnetic flux density	Under high glucose condition, insulin release was inhibited. Under low glucose concentration conditions, SMF can increase insulin levels in a flux density-dependent manner	Hayek et al. (1984)

differential effects on glycemia (Yu et al. 2021). More specifically, we found that neither the 400 mT, 600 mT alternating pole SMFs (Figs. 10.3a, b), nor the ~100 mT upward direction SMF (Fig. 10.3c) reduced blood glucose levels, while the ~100 mT downward direction SMF (Fig. 10.3d) could reduce blood glucose. Furthermore, most of studies showing elevated glycemia levels and reduced insulin levels in non-diabetic animals have used a 128 mT SMF exposure system (Fig. 10.3g) by the Lake Shore electromagnets device manufactured by Lake Shore Cryotronics, Inc. (Tables 10.4 and 10.5). Interestingly, the direction of SMF generated by their device is vertically upward, which reinforce our hypothesis that the upward direction SMF has a tendency to increase glycemia. Moreover, the magnetic flux density also matters because Hayek et al. found that the release of insulin is dose-dependent with magnetic flux density (Hayek et al. 1984).

Secondly, the biological sample differences contributed to the experimental inconsistencies. This point has also been brought up and reviewed in Chaps. 1 and 3 of this book. As far as we know from Tables 10.1 and 10.2, several types of diabetic animal models have been used to evaluate the effects of SMFs on glycemia or insulin. Some studies use chemical-induced diabetic models, for example, STZ or alloxan, while others use genetic diabetic animals of different strains. For example,

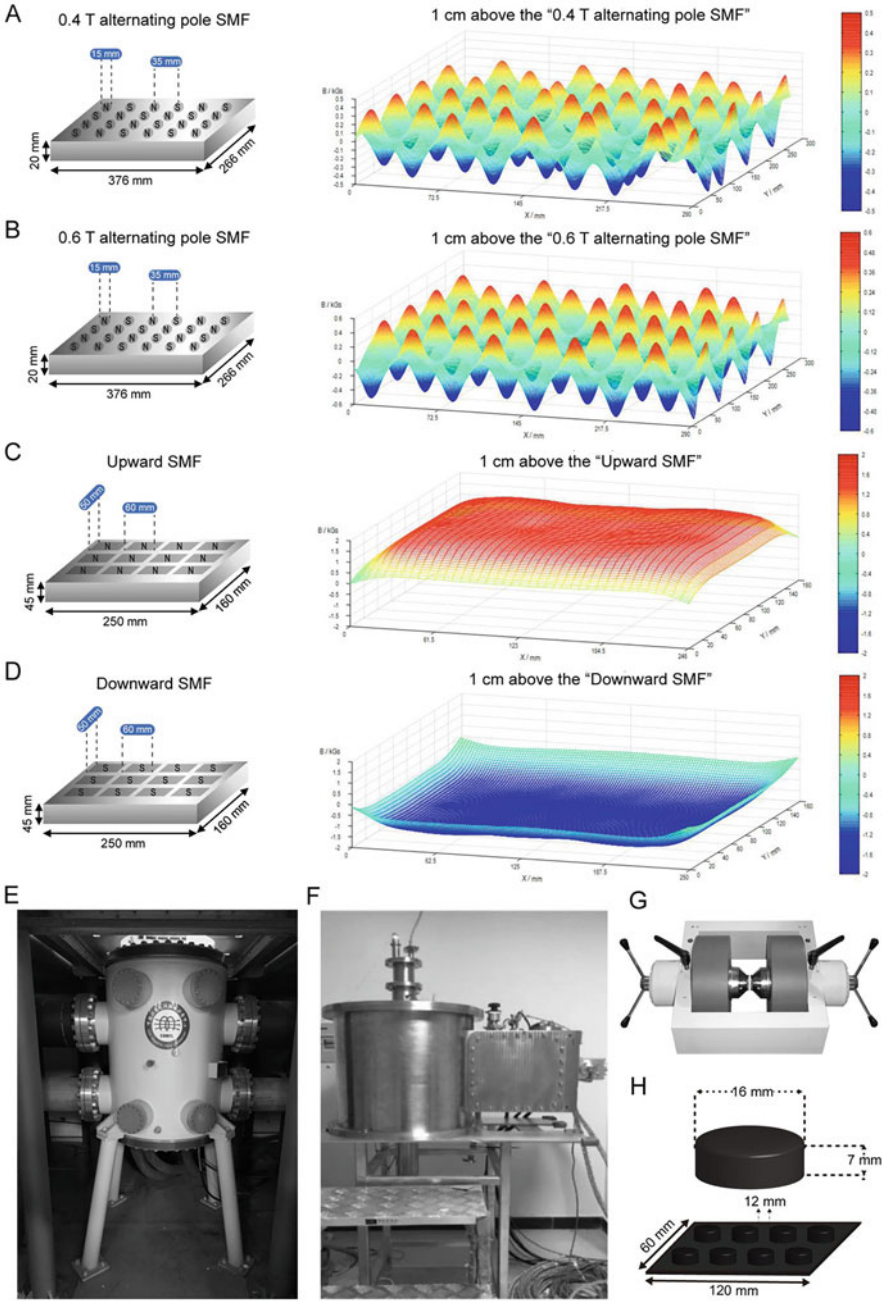

Fig. 10.3 Examples of apparatus that have different static magnetic field settings. (**a**, **b**) Experimental setup and magnetic field distribution for mice exposed to 0.4 T and 0.6 T inhomogeneous SMFs provided by alternating pole magnets (Yu et al. 2021); (**c**, **d**) Experimental setup and magnetic field distribution for mice exposed to upward and downward quasi-uniform SMFs (Yu et al. 2021); Figures were adapted from (Yu et al. 2021), open access. (**e**) A water-cooled magnet (water-cooled magnet #4) in the Chinese High Magnetic Field Laboratory that can provide

by analyzing the results of Yu et al. and Li et al. we found that they used the same magnetic field parameters (alternating pole SMFs of 400 mT and 600 mT), but the glycemia level of T2D mice was different (Li et al. 2020; Yu et al. 2021). We speculate that the mice strain and the modeling methods of the diabetic mice are also important factors. Yu et al. used C57BL/6J mice, whereas Li et al. used ICR mice. And Yu et al. used high-fat chow to feed mice for 6 weeks and then injected 45 mg kg^{-1} of STZ, while Li et al. used high-fat chow to feed mice for 2 weeks and then injected 80 mg kg^{-1} of STZ. In addition, our recent studies found that SMFs also have different effects on glycemia in mild and severe forms of type 1 diabetes (unpublished data). Therefore, since there are multiple diabetes subtypes, and the same type of diabetes also varies based on severity, the exact effects of SMFs are also different.

The third factor is the SMF treatment method, including the duration of exposure, whether to use pretreatment. It has been shown that exposure time is a key factor that contributes to the differential effects of magnetic fields on biological samples. We exposed diabetic mice to SMF for different time points and found that the effects on glycemia are time dependent. After 8 weeks SMF exposure, the glycemia of diabetic mice was not reduced, but after 9 weeks SMF exposure, the glycemia of diabetic mice was significantly reduced compared with the sham control group (Yu et al. 2021). According to László et al. and Li et al. we also found different effects of SMFs exposure time on glycemia (László et al. 2011; Li et al. 2020). In addition, SMF pretreatment may also be an important factor contributing to differences in experimental results. We pretreated the mice with SMF for 6 weeks before they were induced for T2D, whereas Li et al. treated the mice with SMF after they were induced for T2D, which may have contributed to the difference in their results. Finally, whole-body and targeted exposure were also categorized as SMF treatment method, which could also be a potential factor for inconsistencies. From Tables 10.1, 10.2, 10.4, and 10.5, although there is no report using targeted exposure in experiments, the possibility that researchers will not use targeted exposure in the future cannot be ruled out. And we advocate that the effects of SMFs on specific organs, such as the pancreas and liver, should also be explored to discover the specific biological effects of SMFs on specific organs.

Therefore, in order to promote the standardization of related research, we recommend that investigators should carefully design their experiments and accurately describe the experimental details. This includes but not limited to the relevant parameters of the magnetic fields in the experiment (the distance of magnet surface from tissue, exposure time, magnetic flux density, direction, and distribution), and treatment procedure. Besides the basic parameters including body weight, diet, and

Fig. 10.3 (continued) vertical SMFs up to 27.5 T; (**f**) A superconducting magnet in Xin Zhang lab that can provide vertical SMF up to 10 T; (**g**) The Lake Shore device (picture was from the public website: https://www.lakeshore.com/products/categories/overview/discontinued-products/discontinued-products/em4-em7-electromagnets); (**h**) Magnetic plate contains 8 cylindrical permanent magnets of 0.5 T. [Figure was adapted from (Feng et al. 2022), open access]

glycemic change profile in diabetic mice, other assays are also recommended, such as insulin levels and sensitivity, bone mineral density, and angiogenesis markers. The animal sex, age, species, and other key factors should also be clearly recorded.

10.7 Potential Mechanisms for the Effects of Static Magnetic Fields on Glycemia or Insulin

Some preliminary investigations of the potential mechanisms underlying the effects of SMFs on glycemia and insulin have been performed (Fig. 10.4). For example, it was shown that pancreatic islet β-cells can release insulin to reduce glycemia, and SMFs may affect transcription factors and transport channels in pancreatic islet β-cells to regulate insulin secretion (Gorczynska and Wegrzynowicz 1991; Lahbib et al. 2015a; Mao et al. 2017). Some other mechanisms have been proposed, such as iron metabolism, norepinephrine, insulin conformation, cell membrane conformation.

However, it should be mentioned that although these mechanistic study results are listed in Fig. 10.4, it is clear that there is still no consensus model so far. Moreover, most of them are hypothesis-based, and the direct molecular evidence, or more importantly, the physical mechanism is still lacking. In addition, due to differences in the SMF parameters, treatments, and subjects used in these studies, the mechanisms by which SMFs affect glycemia and insulin levels are very diverse. Therefore, in the future, we should systematically study their mechanism and focus more on a biophysical perspective.

10.8 Conclusion

In conclusion, although the regulation of glycemia and insulin levels by SMFs is inconclusive so far due to the SMFs parameter and biological sample difference, it is clear that multiple SMFs treatment modalities have shown significant beneficial effects on diabetic complications, especially the consistently improving effects on diabetic wound healing. In addition, based on current experimental evidences, we have also revealed some clues to optimize SMF parameters to achieve better anti-diabetic effects, including SMF flux density, direction, and distribution. We believe that more systematic and in-depth investigations will definitely help us to unravel the detailed mechanisms of SMF regulation on diabetes and its complications, both biologically and physically, so that we can eventually take the best advantages of SMFs and apply them in the clinical treatment of diabetes.

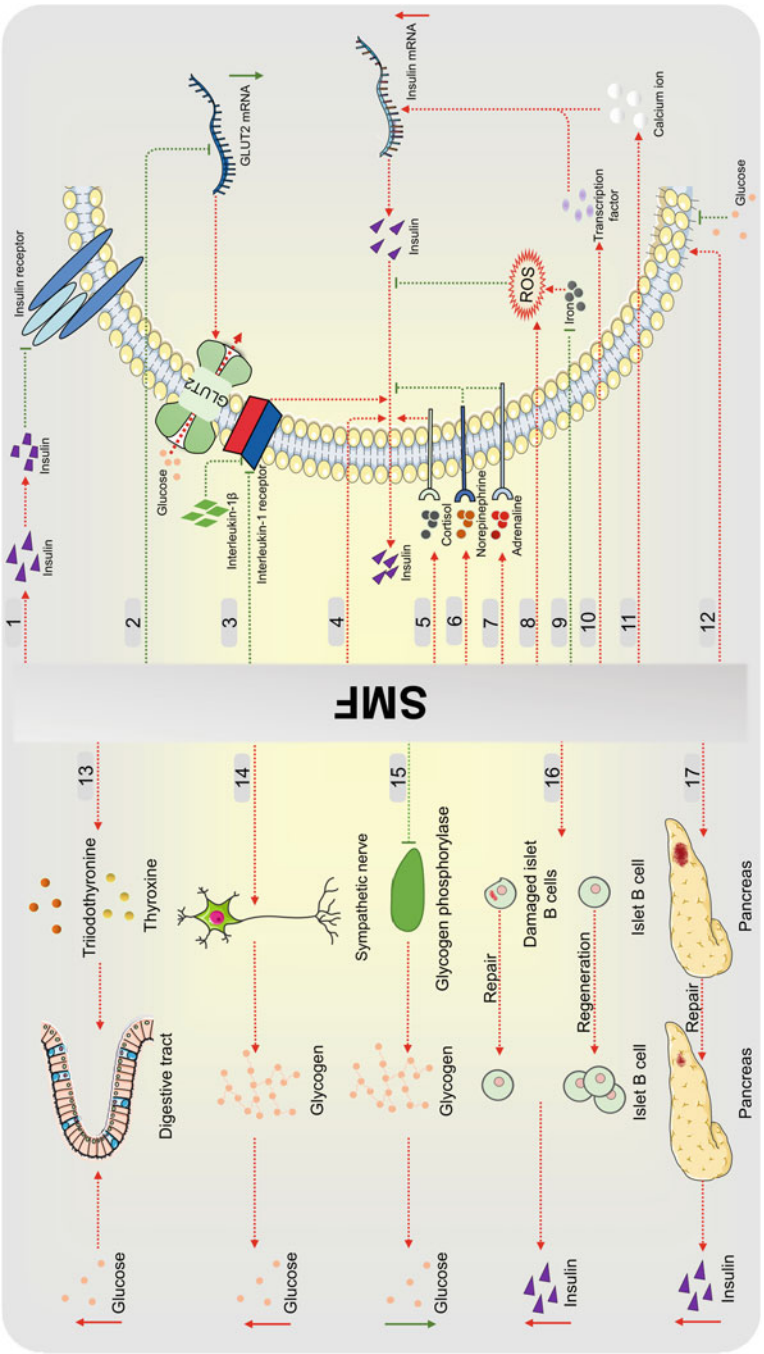

Fig. 10.4 Potential mechanisms for the static magnetic field effects on glycemia or insulin proposed by reported studies. **1.** SMF exposure may change the conformation of insulin, reducing its affinity for the insulin receptor and impairing its function (Elferchichi et al. 2011). **2.** After SMF exposure, GLUT2 expression in pancreatic islet β-cells is reduced, which prevents pancreatic islet β-cells from sensing extracellular glucose concentrations, resulting in cells being unable to release insulin (Lahbib et al. 2015a). **3.** SMF exposure can evoke an effect resembling interleukin-1 receptor antagonist, which may be equivalent to

Fig. 10.4 (continued) insulin intake reducing interleukin-1β level, suppressing the recruitment of innate immune cells, and thus diminishing glycemia (László et al. 2011). **4.** The soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors protein complex can help insulin transport out of cells, and exposure to SMF promotes mRNA expression of synaptosomal-associated protein 25 and synaptotagmin 1, components of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors protein complex, to facilitate insulin release (Mao et al. 2017). **5.** SMF promotes insulin release by increasing cortisol levels (Gorczynska and Wegrzynowicz 1991). **6.** SMF inhibits insulin release and increases glycemia by raising norepinephrine levels (Abdelmelek et al. 2006; Elferchichi et al. 2011). **7.** SMF elevates adrenaline levels (stimulate pancreatic islet B cell α receptors) to decrease insulin release and promote glycemia elevation (Gorczynska and Wegrzynowicz 1991). **8.** SMF increases intracellular ROS levels to reduce insulin secretion (Elferchichi et al. 2010). **9.** SMF restores the abundance of iron complex outer membrane receptor genes in gut microbiota, thus probably allowing dietary iron to enter microbes, reducing iron storage in cells, decreasing oxidative stress caused by excess iron accumulation, and finally restoring insulin secretion (Yu et al. 2021). **10.** SMF promotes insulin gene expression by inducing the expression of multiple transcription factors that bind to the promoter regions of insulin genes (Mao et al. 2017). **11.** SMF contributes to insulin-related mRNA expression and insulin secretion by increasing intracellular calcium concentration (Sakurai et al. 2009). **12.** SMF of defined intensity can change the lipid layer of the cell into the nematic phase, thus constituting a barrier to the diffusive movement of glucose, which is not beneficial to glucose transport to the interior of the cell (Gorczynska and Wegrzynowicz 1991). **13.** SMF elevates thyroxine and triiodothyronine levels (enhance the absorption of glucose in the digestive tract) to induce hyperglycemia (Gorczynska and Wegrzynowicz 1991). **14.** SMF reduces insulin levels by inducing sympathetic hyperactivity (Lahbib et al. 2010). **15.** SMF decreases glycemia by reducing the activity of glycogen phosphorylase and diminishing glycogen breakdown in the liver (Li et al. 2020). **16.** SMF can reduce glycemia by promoting the regeneration and repair of pancreatic islet B cells, protecting pancreatic islet cells, and improving insulin secretion (Li et al. 2020). **17.** SMF can repair the injury of the pancreas and improve the function of pancreatic islet cells to promote insulin secretion (Li et al. 2020). The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license

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