Mind-Body Intervention and Diabetes

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Mind–body intervention (MBI) refers to interventions like meditation, yoga, and qigong, which deal with both physical and mental well-being. MBI not only induces psychological changes, such as alleviation of depression, anxiety, and stress, but also physiological changes like parasympathetic activation, lower cortisol secretion, reduced inflammation, and aging rate delay, which are all risk factors for T2D. Notably, MBI has been reported to reduce blood glucose in patients with T2D.

mind–body intervention epigenetic modification diabetes

1. Epigenetics

Epigenetic mechanisms allow control of gene activity without altering the DNA sequence, and through this process, genes are able to adapt to the changing environment [1]. Epigenetic information is either inherited or acquired. They might exert long-term effects but have been shown to be reversible. Any exposure before and during pregnancy can affect the parental germ cells and the fetus, inducing epigenetic changes. Besides these, the environment or lifestyle could also cause epigenetic changes in an individual. Epigenetic marks can be divided into three main types: DNA methylation, histone modification, and small non-coding RNA. These epigenetic modifications are spatially and temporally controlled and exhibit gene-expression regulatory functions. For example, the addition of methyl groups to cytosine can stimulate chromatin condensation, causing the transcriptional machinery to lose access to DNA, thus suppressing gene expression. The environment of subjects, such as exercise, diet, and stress, can increase or decrease the methylation modification in the target genomic region, followed by reduction or increase in the corresponding gene activity, respectively. For example, six months of exercise intervention increased DNA methylation of some genes in human adipose tissue, including several candidate genes related to diabetes, with a notable decrease in the corresponding mRNA expression [2]. In contrast, Barrès et al. [3] revealed that one bout of exercise reduces the promoter DNA methylation of substrate metabolite genes in the human skeletal muscle, and increases their gene activity. Similarly, acetylation and deacetylation of histones cause chromatin to become loose or tight, respectively, to activate or inhibit gene transcription along the genome. Moreover, microRNA controls the stability of mRNA and access to the translation machinery, thereby affecting protein production [4].

2. Epigenetic Changes and Diabetes

Type 2 diabetes (T2D) is characterized by a chronic increase in blood glucose level, which is caused by inadequate insulin secretion or insulin resistance. Aging, a sedentary lifestyle, and obesity are all well-known contributors to

insulin resistance. The pancreatic islet cells, which secrete insulin, become dysfunctional in insulin regulation after prolonged exposure to high levels of lipids and glucose [5][6].

2.1. Diabetes-Related Epigenetic Changes in Parents, and During Prenatal and Early Life

Notably, individuals with diabetes have been observed to have significant changes related to DNA methylation in the insulin-producing (pancreatic islets) and insulin-targeted tissues (adipose tissue, skeletal muscle, liver). This finding suggests that the epigenetic mark is associated with the incidence of T2D [7][8]. As follows, studies have revealed that these epigenetic marks can be inherited from parents or acquired during fetal or early life and through lifelong environment or lifestyle.

Epigenetic information can be passed on to the offspring by changing the reproductive cells of the parental generation. The pups of male mice on a high-lipid diet exhibited an altered metabolism phenotype, including obesity and beta cell dysfunction [9]. Moreover, environment-induced parental stress can cause epigenetic changes. A restraint stress mouse model revealed that the increased glucocorticoid level of stressed parent mice caused excessive DNA methylation in the *Sfmbt2* gene promoter in sperm cells, which induced hyperglycemia in the offspring by increasing gluconeogenesis through reduced miR-488b-3p expression, followed by enhanced expression of PEPCK [10]. This finding indicated that epigenetic marks acquired due to parental stress conditions can be passed down to their offspring.

The fetus is vulnerable to epigenetic changes depending on the environment. During the fetal development, individuals exposed to conditions such as malnutrition, xenobiotic expansion, substance use, placental insufficiency, gestational diabetes or prenatal stress have been noted to have abnormalities in glucose and lipid metabolism besides a higher risk of developing T2D [11]. A rat model revealed that a mother's low-protein diet changed the expression of certain transcription factors in the fetal pancreas, inhibiting beta cell proliferation and promoting cell differentiation [12]. Consequently, the number of beta cells decreased in the offspring, thereby increasing the risk of T2D during adulthood. Similarly, several reports have implied that intrauterine exposure increases the risk of T2D in humans. Children born to mothers with T2D during pregnancy were more likely to develop T2D and obesity than those born to non-diabetic mothers [13][14]. Moreover, people exposed to famine during fetal stage were noted to have glucose intolerance in adulthood [15].

Maternal antenatal stress has also been noted to affect body weight and glucose metabolism in the offspring [16]. According to a meta-analysis, body mass index (BMI) (18 studies) and body fat (5 studies) were significantly higher when under fetal stress [17]. In the placenta, HSD11B2 exists to reduce exposure to the maternal glucocorticoid hormone, converting cortisol or corticosterone into inactive metabolites. However, the maternal stress experienced during the prenatal period can induce an increase in DNA methylation of certain CpG sites located in the *HSD11B2* gene promoter and downregulate expression of the enzyme in the placenta [18]. Notably, both human and animal models have observed epigenetic changes after prenatal stress in fetuses and children [18][19] including methylation changes of the glucocorticoid receptor gene (*NR3C1*, receptor for cortisol). For example, changes in *NR3C1*

promoter methylation were detected in the cord blood of newborns born to a mother with depression during pregnancy [20]. Moreover, newborns exposed to prenatal stress were noted to have methylation in the *NR3C1* promoter in umbilical cord blood samples [21].

The risk factors of T2D were evidenced to be induced not only by the lifestyle during adulthood, but also by the living conditions during early life [22][23]. The epigenetic mechanism associated with the regulation of gene expression plays a crucial role in mediating the connection between early-life adverse conditions and the risk of chronic diseases (including T2D) occurring in the later years of life [24]. Notably, these effects are not solely limited to physical adversity, but also include mentally harmful environments during development. Early-life adversity, such as childhood abuse, consistently exhibits a condition wherein inflammation develops, because of regulatory dysfunction in the inflammatory pathway over a prolonged period of time [25][26]. Chronic mild inflammation is critically associated with the incidence of T2D [27]. Early-life experiences might significantly affect aging-related phenotypes through the epigenetic factors and potentially influence other aging-related diseases [11].

2.2. Psychological Stress and Type 2 Diabetes

2.2.1. Psychological Factors Related to Type 2 Diabetes

Psychological stress (including depression, anxiety, and anger) is commonly associated with several physical diseases and has been increasingly recognized as a risk factor for disease onset and progression. Studies have suggested that stress plays a causative role in T2D, serves as a predictor of T2D onset, and acts as a prognostic factor in patients with conventional T2D [28]. This finding could be because glucose homeostasis is affected by the cortisol produced by the hypothalamic–pituitary–adrenal (HPA) axis activation during stress [29]. Moreover, psychological stress can reduce the motivation of individuals to sustain a healthy lifestyle. In a study which followed 7000 healthy adults for 10 years, the perceived stress was related to unhealthy behaviors such as physical inactivity, unsuccessful smoking/alcohol cessation attempts, and T2D incidence [30].

Depression is the most studied psychological factor in the field of diabetes. A meta-analysis of people with diabetes revealed that comorbid depression increased the non-adherence to healthy behaviors related to diet, medication, and exercise [31]. Therefore, the unhealthy effects of depression on these behaviors are likely to be detrimental to people with diabetes. Notably, meta-analysis and prospective cohort studies suggest that depression is associated with an increased risk of diabetes [32][33][34]. In addition, depressive symptoms, including lack of joy, despair, and a diagnosis of clinical depression, are considered predictive factors in the development of diabetes [33][34]. Furthermore, negative personality traits, such as anger, have been studied regarding T2D development [35][36]. A 6-year longitudinal study involving 11,615 non-diabetic adults revealed that anger was associated with a high risk of future T2D development [35]. Furthermore, an 11.4-year study involving 5598 adults (no T2D or cardiovascular disease) revealed that anger and anger response significantly increased the T2D risk [36], indicating that anger is a risk factor for developing diabetes.

Positive psychological factors also seem to affect the glycemic control. A study involving 111 patients with diabetes (both type 1 and 2 diabetes) examined the longitudinal relationship between resilience and glycemic control and

noted that low stress resilience further aggravated a 1-year follow-up Hemoglobin A1c (HbA1c, glycated hemoglobin) in both types of diabetes [37]. In a longitudinal study involving 97 elderly women (without diabetes), the relationship between positive well-being and glycemic control was investigated [38]. Those with greater positive well-being at baseline exhibited a statistically lower level of HbA1c at a 2-year follow-up. These results suggest that negative psychological factors, such as depression, anger, and low stress resilience increase the risk of diabetes, whereas positive psychological factors, such as positive well-being, have the opposite effect. Psychological stress causes physiological changes through three major pathways, namely the neuroendocrine (cortisol), autonomic, and inflammatory pathways. Therefore, it seems that psychological stress functions through these pathways when it acts as a risk factor for diabetes [28].

2.2.2. Cortisol and Type 2 Diabetes

Corticosterone is a primary glucocorticoid in the physiological stress-response system of rodents [39]. Notably, in rodents, chronic administration of corticosterone induces hyperglycemia, insulin resistance, and dyslipidemia [40] [41]. In humans, cortisol, a glucocorticoid hormone, is secreted from the adrenal cortex as an output of the HPA axis during stress. Chronic activation of the HPA axis leads to dysregulated cortisol output [42]. Glucocorticoid receptors are expressed in the pancreatic beta cells that secrete insulin, and thus, cortisol stimulation directly affects insulin sensitivity and reduces insulin secretion [43]. Therefore, abnormal cortisol secretion can cause problems with blood glucose regulation, which is why patients with Cushing's syndrome, those with chronic excessive cortisol secretion [44], and those taking glucocorticoids prescription [45] are often noted to have a high vulnerability to hyperglycemia and have a higher risk of developing diabetes mellitus. A longitudinal study involving 3270 healthy people observed that high levels of evening cortisol were associated with the likely development of T2D within 9 years [46]. Besides the incidence of T2D, upon considering the prediabetic condition (impaired fasting glucose) into the analysis, elevated evening levels of cortisol and a flatter slope of cortisol across the day were noted to be predictive factors of diabetes. However, morning levels of cortisol and cortisol awakening response were not related to T2D onset [46].

2.2.3. Autonomic Nervous System and Type 2 Diabetes

Stress-induced sympathetic activation causes changes in blood pressure, heart rate, and cardiac output, which are recognized risk factors for diabetes [47]. A study involving a cohort of 4.1 million adults who did not have diabetes or cardiovascular disease investigated the link between diabetes risk and blood pressure, using the electronic health record connected to the United Kingdom primary care system, and revealed that systolic and diastolic blood pressures were both risk factors for developing diabetes mellitus [48]. Besides blood pressure, an increased resting heart rate and a decreased heart rate variability were considered to be risk factors for T2D. A meta-analysis that investigated 10 cohort studies (120,000 participants) showed a positive relationship between resting heart rate and incident of T2D [49]. Changes in the autonomic nervous system (increased sympathetic nervous system and decreased parasympathetic nervous system), which increased the risk of T2D, were associated with metabolic syndrome [50], and decreased heart rate variability (markers of autonomic nervous system control) was associated with increased levels of fasting blood glucose (FBG), cortisol, and expression of pro-inflammatory cytokines [51].

2.2.4. Inflammation and Type 2 Diabetes

Chronic inflammation resulting from abnormal immune system activation is a risk factor for diabetes mellitus. T2D is considered a chronic low-grade inflammatory state associated with multiple inflammatory mechanisms and metabolic pathways [52]. Studies have revealed that circulating concentrations of pro-inflammatory adipokines are increased in patients with T2D. For example, a study involving 15,000 people in Germany reported a dose–response relationship between the impaired glucose status and adipokine concentrations [53]. In addition, a meta-analysis involving 10 prospective studies revealed that an increased concentration of inflammatory cytokines, interleukin (IL)-6, and C-reactive protein (CRP) in the circulatory system was associated with increased risk of future T2D [54]. Indeed, in patients with T2D, the biomarkers indicating chronic inflammation are repeatedly detected in the pancreas, liver, fat tissue, and white blood cells [52].

2.2.5. Complications

Studies suggest that psychological factors, especially depression, increase the risk of complications from T2D. Patients diagnosed with diabetes and depression have higher risk of microvascular [55][56], macrovascular comorbidities [57][58][59], and mortality [60]. Notably, these vascular complications in patients with diabetes appear to be linked to epigenetic changes [61][62][63]. For example, in the genome-wide DNA methylation profiles of DNA isolated from whole blood of myocardial infarction patients or control subjects, two DNA methylation sites were identified to be significantly correlated with myocardial infarction [63].

2.3. Aging and Type 2 Diabetes

T2D is considered a typical aging-related disease because it generally emerges after the age of 40 years. Because conditions associated with aging processes (e.g., inflammatory states) are characteristics of both T2D and aging [64], T2D is conceptualized as early maturity or accelerated aging [65]. Notably, epigenetic changes are strongly associated with aging. The genome either gains or loses methylation over time. Fraga et al. [66] noted that the epigenome in the cells of young identical twin pairs is similar, whereas the epigenome diverges in the older identical twin pairs, indicating the effect of age on DNA methylation. Moreover, DNA methylation of 3470 sites was revealed to be changed in common across various cell types (fat tissue, liver, and blood) during aging [67]. In addition, in several genes (*FHL2*, *ELOVL2*, *KLF14*) associated with T2D, the methylation of CpG sites were noted to be similarly affected in all investigated tissues.

2.4. Lifestyle and Type 2 Diabetes

Over the past few decades, the incidence of T2D has dramatically increased worldwide. Rather than being explained by genetic changes, it is suggested that this was induced by rapid changes in lifestyle globally [68]. According to the study which meta-analyzed nine trials regarding the correlation between total daily sitting time and cardiovascular disease or diabetes in 448,285 participants, it was found that daily sitting time was positively correlated with an increased risk of cardiovascular disease and diabetes [69]. Therefore, a sedentary lifestyle seems

to increase the risk of cardiovascular problems and diabetes. Therefore, unhealthy lifestyles, including unhealthy eating, lack of exercise, and smoking, often exacerbate biological changes induced by chronic stress [70].

3. Types of Mind–Body Intervention and Their Effects

Mind–body intervention (MBI, also known as mind–body training, mind–body practices, and mind–body therapy) refers to meditation, yoga, and tai chi that deal with both physical and mental well-being [71][72]. These interventions are performed with the goal of gaining positive influence on overall health by fostering mental serenity, mental care, and critical cognition, as well as by improving body function through breathing and physical movement. MBI can be categorized into static methods (sitting meditation), dynamic methods (moving meditation), and a combination of both. Static methods can include mindfulness meditation, Vipassana, transcendental meditation (TM), Zen meditation, Buddhist meditation, Sudarshan Kriya, Kirtan Kriya, Pranayama, and relaxation response. Mindfulness meditation is a well-known way to cultivate a state of mindfulness in everyday life [73]. TM is a form of silent mantra meditation with one's eyes closed [74]. Relaxation response is a simple, secular version of TM [75]. Zen meditation, one of the Buddhist practices, is the practice of sitting cross-legged, concentrating on the mind, and contemplating quietly, and it suspends all judgmental thinking and letting words, ideas, images, and thoughts pass by without getting involved in them [76]. In terms of content, the static method can be divided into open monitoring meditation (e.g., mindfulness meditation) and focused attention meditation (e.g., TM, brain wave vibration).

Dynamic MBIs include movement meditations, such as yoga, tai chi, and qigong, which can be considered a combination of mindfulness intervention and physical activity [77]. Yoga is a group of physical, mental, and spiritual practices or disciplines, largely consisting of different yogic postures [78]. Tai chi is a moving meditation involving a series of slow, gentle motions that are patterned on the movements in nature. Qigong is often referred to as the "internal" portion of tai chi and is characterized by stationary movements that are repeated a certain number of times.

Combined protocols involve a mix of both static and movement meditations. Mindfulness-based stress reduction (MBSR) is an 8-week integrated training consisting of mindfulness meditation, concentrative meditation, breathing exercises, yoga, autogenic training, and Buddhist philosophy [79]. It blends various techniques and is referred to in the clinical setting as mindful awareness practices [80], mindfulness-based movement [81], mindfulness-based interventions [73], and so on. Buddhist walking meditation is a way of walking with a sense of awakening to one's body and awareness of the surrounding environment [82]. Brain wave vibration meditation (also known as brain education meditation (BEM)) is a combination of static and dynamic methods that manages health of body and mind based on the following five steps: (1) Brain sensitizing (activating the connection between the body and the brain through various body movements), (2) brain versatilizing (making one's body flexible through yoga, breathing exercises), (3) brain refreshing (brain wave vibration, energy dance), (4) brain integrating (imagery meditation, body scan), and (5) brain mastering (philosophy of enlightenment) [83][84].

MBI has been reported to relieve stress-dependent symptoms of various diseases, including psychological disorders (mood and anxiety disorders), inflammatory diseases, aging, and cancer [80][85][86]. The incidence and

progression of diabetes can be affected by stress [46]. Therefore, MBI can be beneficial especially in patients with diabetes. In this work, we explored how MBI affects the incidence and progression of diabetes, as well as exploring its mechanisms, with a special focus on the epigenetic mechanisms.

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