Treating depression in diabetic patients: *Latihan pasrah diri (LPD)* revisited

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ABSTRACT

The condition accompanying depression will always be progressing into poor prognosis if the depression itself is not recognized and treated properly. Among diabetic patients, depression was associated with increased mortality and poor quality of life . It was observed that diabetes and depression has a bidirectional relationship, where the clinical course of both conditions are affecting each other. Despite the effectiveness of psychological and psychopharmacological interventions in treating depressive symptoms in diabetic patients, the effect of such interventions on glycemic control is still inconsistent. Complementary alternative medicine (CAM) alone or in combination with standard medical treatment, targeting both depression and diabetes, appears to be promising. Latihan Pasrah Diri (LPD) has been recognized as a type of relaxation technique under CAM. It is initially directed to provide adequate relieve of depression using both religious and relaxative approach. Among patients with comorbid diabetes and depression, this approach has long been known and utilized over the counter, but its formal practice is seldom advocated, whereas, many clinical trials has been conducted locally to reveal its potential use. Combined with standard therapy, LPD is expected to show its beneficial effects.

Keywords: depression, diabetes, complementary alternative medicine, *latihan pasrah diri*

ABSTRAK

Kondisi yang menyertai depresi akan selalu berlanjut menjadi prognosis buruk jika depresi itu sendiri tidak dikenali dan diobati dengan baik. Di antara pasien diabetes, depresi dikaitkan dengan peningkatan angka kematian dan kualitas hidup yang buruk. Diobservasi bahwa diabetes dan depresi memiliki hubungan dua arah, di mana perjalanan klinis kedua kondisi tersebut saling mempengaruhi. Terlepas dari efektivitas psikoterapi, efek dari intervensi kontrol glikemik tersebut masih tidak konsisten. Pengobatan alternatif komplementer (CAM) sendiri atau dikombinasikan dengan pengobatan standar, yang menargetkan depresi dan diabetes, tampaknya menjanjikan. Latihan Bela Diri (LPD) telah dikenali sebagai jenis teknik relaksasi di bawah CAM. Ini pada awalnya diarahkan untuk memberikan bantuan depresi yang memadai dengan menggunakan pendekatan religius dan relaksasi. Di antara pasien diabetes komorbid dan depresi, pendekatan ini telah dilakukan dan jarang dianjurkan, sedangkan banyak uji klinis telah dilakukan secara lokal untuk mengungkapkan potensi penggunaannya. Dikombinasikan dengan terapi standar, LPD diharapkan dapat menunjukkan efek menguntungkannya.

Kata kunci: depresi, diabetes, pengobatan alternatif komplementer, latihan self-absorption

A. Introduction

Depression is common in diabetes and has been shown to cause detrimental medical outcomes. The field of research to find treatment that consistently leads to better medical outcomes in patients with both depression and diabetes is still widely open. LPD was introduced to complement psychological and psychopharmacological therapy in this area. This review provides brief insight of recently published, randomized

controlled trials (RCTs) on the treatment of depression in diabetic patients, revisiting LPD as a novel therapeutic modality under CAM.

Mapping the Problem

The prevalence of depression is 2–3 times higher in people with diabetes than in the general population with approximately 10% of diabetes patients have major depression (1). The fact that adults with depression have also an increased risk of developing type 2 diabetes (37% increased risk) (2), leave us to conclude that there is a bidirectional association between depression and diabetes (3,

4). The mechanisms behind this association is unclear. In one direction, at least three hypothesis have been proposed, including: depression resulting from the psychosocial burden of living with diabetes; depression resulting from biochemical changes related to diabetes and its treatment; and depression and diabetes are highly prevalent diseases that coexist solely by chance (5). The results of two recent studies have proven the opposite direction that depression preceded and predisposed people todiabetes (6, 7), yet with unclear mechanism. One might argue that depression is often accompanied by poor health behaviors (i.e., smoking, physical inactivity, uncontrolled caloric intake) that risks individuals to develop type 2 diabetes (8). Depression is also associated to central obesity and impaired glucose tolerance (9). In addition, depression is well known to be linked to physiological abnormalities, including activation of the hypothalamic-pituitary-adrenal (HPA) axis, sympathoadrenal system, and pro-inflammatory cytokines, which induce insulin resistance and eventually contribute to diabetes incidence (10).

It is also becoming increasingly clear that the relationship between depression and diabetes as being different for type 1 and type 2 diabetes (11). For example, a recent systematic review of the literature on depression in type 1 diabetes found no evidence of increased rates of depression in people with type 1 diabetes (12) whereas the data in type 2 diabetes clearly show higher rates of depression (13). This indicates future direction that the therapy option might be different.

In patients with diabetes, depression is associated with higher mortality and higher risk of major complications (14-16). Furthermore, patients with diabetes and depression reported a poorer quality of life (17), reduced well-being (18), higher diabetes-related distress (19, 20), lower diabetes treatment satisfaction (21), reduced diabetes self-care (22), and higher non-acceptance of diabetes treatment modality (23). All of these combined would further add lethal effects on the outcome .

The mechanisms explaining depression to increase morbidity and mortality are not fully understood. Not only behavioral factors such as poor self-care (22), pro-inflammatory mechanisms are also considered responsible . Howren et al. (24) reported that depression is associated with elevated circulating levels of C-reactive protein and interleukin (IL) -6, serve as pro-inflammatory mediators, as well as higher levels of the counter-regulatory IL-1 receptor antagonist (IL-1RA) (25, 26). Therefore, subclinical inflammation may be a reasonable mechanism translating poorer prognosis in individual with depression and diabetes, not surprisingly because the aforementioned inflammatory markers are also associated with diabetes complications (27).

Despite the effectiveness of psychological and psychopharmacological interventions in treating depressive symptoms in people with diabetes , their effects on glycemic control

remain inconsistent. In the psychosocial or mixed intervention arm, Petrak et al. (28) reported that both cognitive behavioral therapy and sertraline did not improve glycemic control in patients with depression and poorly controlled diabetes. Likewise, Hermanns et al (29) showed that diabetes specific-cognitive behavioral therapy in patients with depression and diabetes did not improve HbA1c. However, both studies did show significant improvement in depression scale. In contrast, Safren et al. (30) reported that cognitive behavioral therapy for adherence and depression trial (CBT-AD trial) improved HbA1c, adherence, and depression symptom in type 2 diabetic patients. Similarly, an integrated care intervention consisting education, guideline-based treatment recommendations and monitoring of adherence and clinical status demonstrated improvement of depression, significant reduction of HbA1c level, and better adherence (31). But, another systematic review and meta-analysis of collaborative care in 2,238 diabetic patients with depression (32) failed to document a significant reduction of HbA1c le vel. This later data further confirmed inconsistency of psychosocial or mixed intervention in improving glycemic control.

Psychopharmacological intervention did show good results in reducing depression symptoms in diabetic patients. However, variable results on glycemic control was observed, similar with psychosocial or mixed intervention. Nortriptyline (a tricyclic antidepressant) has led to worsening of glucose control indices, whereas fluoxetine and sertraline (both selective serotonin reup take inhibitors [SSRIs]) consistently produce reduction of glucose levels (33).

Fair amount of ongoing researches is being awaited to better provide efficacious option in the treatment of depression in diabetes. Interestingly, CAM that has gained a lot of attention among patients with chronic diseases, is now increasingly used in treating patients with depression. It is now the 10 most frequent modalities used to treat depression (34). Herbal remedies, acupuncture, homeopathy, massage, relaxation, and unconventional psychotherapeutic approach have been reported as the most prevalent CAM among psychiatric patients (35). Diabetic patients are also familiar with CAM, not surprisingly, because diabetes health professionals use or recommend CAM to people with diabetes. For example, Sabo et al. (36) surveyed 2,850 American diabetes educators about their CAM use and achieved a response rate of 829. Not only people with diabetes use CAM to improve glycemic control, but they also use it for a range of other reasons, such as prevention, to manage distressing symptoms such as pain associated with complications, and to improve their quality of life (37). Leese et al. (38) found 17 % of people with diabetes attending an outpatient clinic in the United Kingdom used CAM. Egede et al. (39) extracted data from a United States Medical Expenditure Survey and estimated that people with diabetes have odds of 1.6 times to use CAM than non-diabetics and suggested that diabetes is an independent predictor of CAM use in people over 65 years.

LPD as one form of CAM, has been studi ed extensively in Yogyakarta, Indonesia. It consists of the combined practices of relaxation and dhikr focusing on breathing exercise and the meaning of the words spoken during dhikr (repetitive prayer and guided imagery) as a self-management technique that was believed could evoke relaxation response. It was hypothesized that relaxation response would decrease stress response or depression symptoms , which in turn improve glycemic control (40). The effects of LPD on inflammatory mediators, metabolic marker, and various clinical relevance in depression patients with diabetes were also studied. The results are potentially promising, making it possible to target both depression and diabetes to improve concurrently with one key therapeutic approach.

Current Evidence from Randomized Controlled Trials (RCTs): What Do We Have Now?

As a brief example, the search of current RCTs (June, 2016) in PubMed database published for the past

5 years with keyword diabetes and depression reveal ed at least 20 results of RCT in diabetic patients with depression. The RCTs consisted of psychopharmacological intervention, psychosocial intervention, or combination of both. What we do have now is a broader option to effectively treat depression in diabetic patients, yet still with limitations regarding glycemic control . Some of the results has been cited above. Interestingly there are fair amount of studies consisted of only psychosocial interventions, whereas few studies addressing CAM use.

Complete literature review had been published in 2009 by Petrak et al. (41) and in 2011 by Markowitz et al. (42) with extensive discussions and details concerning each RCT. Therefore, we are not coming with such a 2016 review, but more to describe concisely what we have reach ed until now. The followings are interventions found in the PubMed databases: stepped care interventions (43), depression care management (44), algorithm-based care (45), multifaceted psychiatric intervention (46), interpersonal psychotherapy (47, 48), cognitive behavioral therapy (CBT) (28-30), collaborative care (32, 45, 49, 50), nurse-led case manager (51), addition of fish oil to antidepressants (52), psychoeducation and physical exercise (53), integrated primary care (31), intensive lifestyle intervention (54), acceptance facilitating intervention (55), and integrated care management (31). Psychopharmacological therapies found in PubMed include s-citalopram (56), fluoxetine (57), paroxetine (58), sertraline (59), agomelatine (60), and nortriptyline (61).

None of the RCTs involved CAM as the primary intervention, nor in combination with psychopharmacological or psychosocial intervention , except one study that evaluate the use of fish oil to complement antidepressant use (52). In contrast, patients with diabetes and or depression frequently use CAM in the out-clinic setting (34, 38, 39). Moreover, there are growing evidences for beneficial effects of CAM in depression, including exercise, herbal medicines (Hypericum perforatum), acupuncture, and relaxation therapies (11). Although further research involving RCT is still needed to better evaluate the effect of those modalities, the role of CAM in the setting of diabetes and depression cannot be ruled out.

As mentioned above, LPD as one form of relaxation therapy under CAM appears to have a potential role in the treatment of diabetic patients with depression. Considerable amount of RCTs have been conducted locally in regard of LPD among diabetic patients with depression. The intervention used in most of the RCTs was either LPD alone or in combination with psychopharmacological intervention. To date, there are 48 studies published by Gadjah Mada University in Yogyakarta Indonesia evaluating the efficacy of LPD in various clinical settings, and at least 11 of them involved diabetic patients with depression symptoms.

Psychopharmacological Intervention

The impact of antidepressant use on glucose regulation are variable, from hypoglycemic, hyperglycemic or neutral effects, depending on the specific type of the drug. The mechanisms are thought to be related to insulin sensitivity as the main effector, while other reports showed possible interaction with hypoglycemic agents (62).

SSRIs have a beneficial and synergistic effect on both mood and HbA1c levels in diabetes patients with depression. An open-label study administered sertraline at a dose of 50 mg/day to 28 patients for a 10-week period (63). During that time, in addition to reducing the scores on the Hamilton Depression.

Rating Scale (HDRS) ($p < 0.001$) and the Beck Depression Inventory (BDI), dietary compliance rose ($p <$

0.005), and HbA1c levels generally improved. More recently, a double -blind, placebo-controlled study was completed with fluoxetine (57). In that study, a maximum dose of 40 mg/day was received by each of 60 participants for an 8-week period. The differences in response (fluoxetine vs. placebo) were significant for both HDRS ($p = 0.01$) and BDI ($p = 0.03$). HbA1c levels improved more on fluoxetine than on placebo but results did

not reach significance. This was probably because the trial lasted only 8 weeks.

In the other RCT of SSRI, 49 mildly depressed patients wit h non-optimally controlled type 2 diabetes patients were randomized to six months of paroxetine or a placebo (58). No significant differences in HADS scores between the groups was observed. Three months later, HbA1c levels were found lower in patients in the paroxetine than in the placebo group ($p = 0.018$), but were not maintained at six months. It is interesting that this study included only patients with non-optimally controlled diabetes so that the opportunity to demonstrate improvement in glucose control could be potentiated, and at least, satisfyingly explained the difference observed between groups.

Another recently published open-label study of SSRI treatment diabetes patients with depression has been conducted (56). Researchers gave patients with comorbid major depression (assessed by the Structured Clinical Interview for DSM Disorders [SCID] and HDRS score ≥ 16) and type 1 or type 2 diabetes, an open-label s-citalopram therapy for up to 16 weeks. A significant reduction in mean HDRS scores and a limited non-significant decrease in HbA1c levels (–0.36%) was observed. This adds more information regarding the effectiveness of SSRIs in depressed diabetic patients, though without control group the re sults need more replications and extensions.

In relation with hypoglycemia, nefazodone, an antidepressant that can block 5-HT reuptake but predominantly appears to act by blocking postsynaptic 5-HT receptors, has been reported to produce hypoglycemic attacks that led to a reducti on in insulin dosage by 15% (64). Another antidepressant called monoamine oxidase inhibitors (MAOIs), as shown in case reports back in 1960, can cause extreme hypoglycemic episodes (65). Other agent, the noradrenergic antidepressant, maprotiline, has also been shown to cause hypoglycemia even at low doses, which was consistent with the laboratory studies (66). Fluoxetine has also been shown through case report to cause hypoglycemia, hypoglycemia unawareness, and increased insulin sensitivity (62). Another SSRI, sertraline, has been demonstrated to reduce postprandial hyperglycemia in rats and to induce the hypoglycemic effects of sulfonylurea agents in humans. It has not been reported to cause hypoglycemia independently, but in a case report by Pollak et al. (67), a non-diabetic patient with multiple episodes of hypoglycemia during sertraline therapy, had resolved after discontinuation of sertraline.

Nortriptyline, on the other hand, was shown to have a potentially antagonistic effect; while it improves depressive symptoms, it adversely affect glucose control by promoting hyperglycemia (61). Imipramine administration, in a series of case rep orts in 1960, showed that although short-term dosing led to a fall in FPG, long-term administration significantly increased baseline values of fasting plasma glucose (25).

There was one published study of another antidepressant in patients with diabetes and de pression. Lustman et al. (68) administered an open-label bupropion for 10 weeks to the enrolled 93 patients with type 2 diabetes and major depression; the depression was remitted in 63 patients (84%) whom then were followed for an additional 24 weeks. It was found that Body Mass Index (BMI), body fat, and HbA1c levels decreased significantly in the first attempt, and that these changes maintained during follow-up.

While antidepressants may have an important role to play in the treatment of depression in diabetes, there is also some cause for concern. Use of anti -depressant medications was shown to be associated with increased risk of developing diabetes who are alre ady at elevated risk for diabetes (overweight, high fasting glucose, and impaired glucose tolerance) (69). Antidepressant use was also shown to be related to cardiovascular disease risk factors (e.g., e levated blood pressure and dyslipidemia), independent of depression symptoms (70). This warrants precaution of using antidepressants, not only the short term side effects that deserve more attention, but also the long term risks on cardiovascular and diabetes outcome.

Complementary Alternative Medicine in Depression and Diabetes

The term 'complementary therapies' is actually an umbrell a term that encompasses more than 300 different modalities. It tends to diverse and encompasses various health practices or approaches, which are self-defined by the users and applied on their own or in combination with conventional medicines. The two systems can be separate with one system dominant but also they can complement each other (37).

According to WHO, traditional medicine was defined as "diverse health practices, approaches, knowledge and beliefs incorporating plant, animal, and/or mineral -based medicines, spiritual therapies, manual techniques and exercise applied singularly or in comb ination to maintain well-being, as well as to treat, diagnose or prevent illness ". Thus, the terms "complementary" and "alternative" (and sometimes also "non-conventional" or "parallel") are used to refer to a broad set of health care practices that are not part of a country's own tradition, or not integrated into its dominant health care system (71).

As well as a range of definitions of CAM, there is a range of ways they are categorized or grouped. For example, the US NIH, as cited by Pawa (37), divided CAM into five main categories:

1. Alternative medical systems such as Chinese medicine and Ayurveda. Chinese medicine was known as 'traditional Chinese medicine' until recently.
2. Mind–body therapies.
3. Biological-based systems such as herbal medicine, which is s ometimes known as phytomedicine
4. Chinese, Kampo (Japanese), Ayurveda (India), North American Indian, and European.
5. Manipulative and body therapies such as massage and chiropractic.
6. Energy therapies.

Until recently there has been limited quality research into complementary medicine, because, as in other areas, funding is difficult to access, research expertise and research mentors are lacking, and there is limited infrastructure to support research. A great deal of the available research is difficult to interpret due to methodological flaws, poor reporting, and a great deal is not conducted in the manner the particular therapy is practiced (72).

Despite those limitations, Ernst et al. (73) reported depression is one of the most common reasons people use CAM. Meanwhile, Egede et al. [37] estimated that people with diabetes are 1.6 times more likely to use CAM than non-diabetics and suggested that diabetes is an independent predictor of CAM use in people over 65 years. To date, although there are numbers of trials addressing CAM in treating diabetes alone or depression alone, there are only few RCTs, if any, addressing CAM in the treatment of both diabetes and depression as one entity. Electronic database search through PubMed and Cochrane Library conducted in June 2016 found no result for RCT in depressive diabetic patients. However, some limited RCT can be found in some internet literature, consisting of small sized study and negative results.

For example, a stress management and relaxation program was evaluated through randomized, wait- list controlled study by Stenstrom et al . (74). Participants were people with type 1 diabetes who were considered as having stress-related difficulties in their daily life and in the management of their diabetes (n = 36). The study delivered 14 sessions of two-hour group meetings, where instructions in stress and stress management, muscle relaxation, mental imaging, and mental goal setting were practiced. There were noted i mprovements in relaxation and tension with the greatest for those having poorest scores at baseline. No improvements in mood or HbA1c were reported.

Similar results were also noted by Surwit et al. (75) in subjects with type 2 diabetes (n = 108). A control group (n = 48) who received five weekly group sessions of diabetes education, was compared to experimental group (n = 60) practicing five sessions of stress management training (consisted of progressive muscle

relaxation [PMR] , skill developing instruction through stress-reducing cognitive and behavioral therapy, and education about the impact of stress to individual's health). Over period of six months, there was no difference in HbA1C improvement between groups. At the subsequent

12-months follow up, improvements were only sustained in the stress m anagement group with a

significant 0.5% reduction in HbA1C. The study found no effect of intervention on perceived stress, anxiety, and general psychological health.

Both of the above study did not specifically mention that the subject had well defined depression, nevertheless, they did mention that the stress management intervention reduce the stress level but not HbA1c. If CBTs satisfied the criteria of CAM, then the results of RCT of CBT ran in the parallel way with stress management therapy (28-30). The results were also in accordance with the review formerly stated regarding psychopharmacol ogical intervention that they favor depression but not consistently glycemic control. Given the lack of RCTs addressing CAM use among depressive diabetic patients, the field of research in this topic is still widely open.

Latihan Pasrah Diri (LPD)

LPD consists of the combined practices of relaxation and dhikr focusing on both breathing exercise and the meaning of the words spoken during dhikr (re petitive prayer and guided imagery) as a self- management technique that was believed could evoke relaxation response. It was hypothesized that relaxation response would decrease stress response or depression symptoms, which in turn improve glycemic control (40).

LPD as a method of relaxation was first introduced to solely treat depression. But now, many of the post graduate students of internal medicine in Gadjah Mada University Yogyakarta interested to study LPD in more extended fashion. As documented in the library of Gadjah Mada University, there are increasing number of studies examine the effect of LPD, not only to depression, but also to the natural course of chronic diseases often accompanying depression, such as diabetes, chronic kidney disease, human immunodeficiency virus (HIV) infection, cancer, chronic obstructive pulmonary disease, hypertension, geriatric malnutrition, and many others.

To mention, LPD was also introduced with religious nuance. The fact that people tend to choose CAM that are congruent with their personal values and beliefs (34) leaves LPD the most suitable approach to be used in religious society. Especially in Indonesia, where the citizens tend to practice Islamic belief in their daily living, LPD unite well with it, not surprisingly, because it consists of repetitive prayer that was long recognized in Isl am as dhikr. Although intercessory prayer has been shown to have no significant effect on medical outcomes after hospitalization in a coronar y care unit (76), it may not be the same with the effect of dhikr performed during LPD to the depressive diabetic patients. At least until now, there is no evidence against its usefulness.

LPD has another component called guided imagery. This component attempts to help people enter into a relaxed state by trying to mentally place themselves in a different situation. In Islamic belief, the same technique is performed during salat, the five times prayer they always perform as the highest obligation for Moslems to worship Allah, God of the Universe. When performing salat, Moslems were taught to consider their selves as if they met Allah directly in a heavenly place. In LPD, patients are taught the same method that they should think and feel like they were in a paradise, releasing all of their sorrows and replace them with positive energy originating from Allah. The instructor of LPD can help the individual through the process, by prompting the m to imagine, and encouraging the individuals to place themselves in such heavenly place with increasing accuracy, by reminding them of the sounds, sights, smells, and feelings that go with paradise. Because in Islam, the description of paradise is given in great details that every Moslem must have known before, the instructor seldom find difficulty to assist the moslem patients. The same thing might apply

to religious non -moslem patients. With time and practices, the individual will not need to use the gui dance provided by the instructor. Guided imagery is a widely used technique, including in the large prospective cohort of Chronic Disease Self-Management Program conducted to help individuals develop their self-management skills (77). The cohort showed positive results in various outcome, underlining the effectiveness of guided imagery in the patient management.

Breathing exercise is also part of LPD. The breathing exercise consists of inhaling, holding, and exhaling breath in a timely manner. It is hypothesized that by holding breath, the partial carbon dioxide pressure in blood will transiently increase, and this gives vasodilating effect in the brain circulation which in turn mediate the relaxation state in the body. By closing the eye, this technique is done simultaneously with guided imagery, where exhaling breath equal to releasing a ll of the sorrows out of the individual's life. One session of LPD consists of 15 – 20 minutes (21 cycle of breathing exercise combined with dhikr and guided imagery) 2 times a day. It is recommended that LPD to be continuously practiced for at least 21 days in order to achieve the expected result.

Dharma (40) reported insignificant decrease of fasting plasma glucose with 2 session/day LPD for 21 days among diabetic patients with depression symptoms compared to controls (n = 36, p = 0,055). However, the fructosamin level was decreased significantly in LPD group (p = 0,01). BDI score were also decreased but failed to reach significance level (p = 0,06). On the contrary, Muin (78) reported that fructosamin level was not decreased significantly in LPD plus fluoxetine group compared to fluoxetine alone group (p =0.902), and neither was the BDI score (p = 0.437).

The effect of LPD in inflammation parameter among depressive diabetic patients was also studied. Rudiansyah (79) and Kusbandono (80) found that LPD had variable effect on C-reactive protein (CRP) level in diabetic patients with depression symptoms. Meanwhile, Widodo (81) reported that leucocyte count was insignificantly lower in LPD group compared to control. Nevertheless, the researchers reported significant improvement of BDI score in LPD group compared to control , save Kusbandono. The influence of LPD to other mediators such as e ndotheline-1 and nitrous oxide among depressive diabetic patients was also evaluated in two other RCTs (82, 83). Both mediators were shown insignificantly lower in the LPD plus fluoxetine group compared to fluoxetine alone group. A larger trial is needed to confirm all of these insignificant results.

In another report, LPD was able to significantly lower blood pressure and pulse frequency (84), a sign of good relaxation responses. LPD was also demonstrated to improve quality of life (assessed with diabetes quality of life clinical trial questionnaire-revised score) and showed positive effect to lower BDI score among depressive diabetic patients (85).

Astin et al. (86) reported potential adverse effects regarding relaxation technique, including intrusive thoughts, fear of losing control, muscle cramps, and spasms. It is postulated that adverse effects came from underprepared individual. Dharma (40) documented 3 out of 18 subjects in his study (15%) had adverse effects during early phase of LPD. The adverse effects reported were autogenic discharge (anxiety, dyspnea, palpitation, pain, and elevated blood pressure) which also had previously been documented and described by Zalaquett and McGraw (87). Adverse effect may occur probably due to the lack of knowledge regarding the proper technique to perform LPD.

The RCTs evaluating LPD in diabetic patients with depression were still limited by the lack of power (high rate of false negative result due to small sample size), difficulty of standardization and funding, incompliance subjects, and some methodological flaw. Once these limitations removed, we might expect that LPD would become a therapy of interest, not only because it is simple and far from expensive, but also the religious nuance that makes people tend to believe that Allah Himself, God of Almighty, directly send the healing to the patients.

Conclusion

The problem of depression in diabetic patients has come into existence and the treatment is expected to improve both depression and diabetes. Despite the effectiveness of available treatments in reducing depression in diabetes, no consistent effects in HbA1c levels were observed. While antidepressants may contribute as a key role in the treatment of depression in diabetes, still some cause for concern remains. They may risk patients to cardiovascular disease or worsening of glycemic control (including hyperglycemia or hypoglycemia). In contrast, psychosocial interventions or CAM, used alone or in combination with antidepressants , variably showed its beneficial effects on both depression and diabetes. To date, the studies regarding CAM in both depression and diabetes are lacking. LPD as a form of CAM introduced in 2005, is still being extensively studied in Yogyakarta Indonesia. It began to show its efficacy in multiple RCTs conducted since 2006. Although the RCTs evaluating LPD in diabetic patients with depression were still limited by the lack of power (small sized sample), difficulty of standardization and funding, incompliance subjects, and some methodological flaw, the potential role of LPD remains to be elucidated. The field of research is still widely open, and more researchers with well-designed trial concept are welcome.

References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes. A meta-analysis. 2001;24(6):1069-78.
2. Knol MJ, Twisk JWR, Beekman ATF, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia. 2006;49(5):837-45.
3. Chen P-C, Chan Y-T, Chen H-F, Ko M-C, Li C-Y. Population-based cohort analyses of the bidirectional relationship between type 2 diabetes and depression. Diabetes Care. 2013;36(2):376-82.
4. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: A meta-analysis. Diabetes Care. 2008;31(12):2383-90.
5. Lustman PJ, Griffith LS, Gavard JA, Clouse RE. Depression in adults with diabetes. Diabetes care. 1992;15(11):1631-9.
6. Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Depressive symptoms and occurrence of type 2 diabetes among japanese men. Diabetes Care. 1999;22(7):1071-6.
7. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type ii diabetes: A prospective population-based study. Diabetes Care. 1996;19(10):1097-102.
8. Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling us adults. General Hospital Psychiatry. 2008;30(2):127-37.
9. Weber B, Schweiger U, Deuschle M, Heuser I. Major depression and impaired glucose tolerance. Exp Clin Endocrinol Diabetes. 2000;108(3):187-90.
10. Golden SH. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. Current Diabetes Reviews. 2007;3(4):252-9.
11. Cradock S, Skinner C. Counselling and relaxation therapies. In: Dunning T, editor. Complementary therapies and the management of diabetes and vascular disease. 1 ed. Cippenham, Wiltshire, Great Britain: John Wiley & Sons Ltd; 2006. p. 161-3.
12. Barnard KD, Skinner TC, Peveler R. The prevalence of co-morbid depression in adults with type 1 diabetes: Systematic literature review. Diabetic Medicine. 2006;23(4):445-8.
13. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with type 2 diabetes: A systematic review and meta-analysis. Diabet Med. 2006;23.
14. Katon WJ, Rutter C, Simon G, Lin EHB, Ludman E, Ciechanowski P, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes Care. 2005;28(11):2668-72.
15. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: A meta-

analysis. Psychosomatic Medicine. 2001;63(4):619-30.
16. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. American Journal of Epidemiology. 2005;161(7):652-60.
17. Goldney RD, Phillips PJ, Fisher LJ, Wilson DH. Diabetes, depression, and quality of life. A population study. 2004;27(5):1066-70.
18. Saatci E, Tahmiscioglu G, Bozdemir N, Akpinar E, Ozcan S, Kurdak H. The well-being and treatment satisfaction of diabetic patients in primary care. Health and Quality of Life Outcomes. 2010;8(1):1-8.
19. Hermanns N, Kulzer B, Krichbaum M, Kubiak T, Haak T. How to screen for depression and emotional problems in patients with diabetes: Comparison of screening characteristics of depression questionnaires, measurement of diabetes-specific emotional problems and standard clinical assessment. Diabetologia. 2006;49(3):469-77.
20. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, et al. Assessing psychosocial distress in diabetes. Development of the Diabetes Distress Scale. 2005;28(3):626-31.
21. Bassett J, Adelman A, Gabbay R, Aňel-Tiangco RM. Relationship between depression and treatment satisfaction among patients with type 2 diabetes. Journal of diabetes & metabolism. 2012;3(7):1000210.
22. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: A meta-analysis. Diabetes Care. 2008;31(12):2398-403.
23. Schmitt A, Reimer A, Kulzer B, Haak T, Gahr A, Hermanns N. Assessment of diabetes acceptance can help identify patients with ineffective diabetes self-care and poor diabetes control. Diabetic Medicine. 2014;31(11):1446-51.
24. Howren MB, Lamkin DM, Suls J. Associations of depression with c-reactive protein, il-1, and il-6: A meta-analysis. Psychosomatic Medicine. 2009;71(2):171-86.
25. Hood KK, Lawrence JM, Anderson A, Bell R, Dabelea D, Daniels S, et al. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care. 2012;35(12):2443-6.
26. Laake J-PS, Stahl D, Amiel SA, Petrak F, Sherwood RA, Pickup JC, et al. The association between depressive symptoms and systemic inflammation in people with type 2 diabetes: Findings from the south london diabetes study. Diabetes Care. 2014;37(8):2186-92.
27. Herder C, Carstensen M, Ouwens DM. Anti-inflammatory cytokines and risk of type 2 diabetes. Diabetes, Obesity and Metabolism. 2013;15(s3):39-50.
28. Petrak F, Herpertz S, Albus C, Hermanns N, Hiemke C, Hiller W, et al. Cognitive behavioral therapy versus sertraline in patients with depression and poorly controlled diabetes: The diabetes and depression (dad) study. A Randomized Controlled Multicenter Trial. 2015;38(5):767-75.
29. Hermanns N, Schmitt A, Gahr A, Herder C, Nowotny B, Roden M, et al. The effect of a diabetes-specific cognitive behavioral treatment program (diamos) for patients with diabetes and subclinical depression: Results of a randomized controlled trial. Diabetes Care. 2015;38(4):551-60.
30. Safren SA, Gonzalez JS, Wexler DJ, Psaros C, Delahanty LM, Blashill AJ, et al. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (cbt-ad) in patients with uncontrolled type 2 diabetes. Diabetes Care. 2014;37(3):625-33.
31. Bogner HR, Morales KH, de Vries HF, Cappola AR. Integrated management of type 2 diabetes mellitus and depression treatment to improve medication adherence: A randomized controlled trial. Annals of Family Medicine. 2012;10(1):15-22.
32. Huang Y, Wei X, Wu T, Chen R, Guo A. Collaborative care for patients with depression and diabetes mellitus: A systematic review and meta-analysis. BMC Psychiatry. 2013;13(1):1-11.
33. Goodnick PJ. Use of antidepressants in treatment of comorbid diabetes mellitus and depression as well as in diabetic neuropathy. Annals of Clinical Psychiatry. 2001;13(1):31-41.
34. Astin JA. Why patients use alternative medicine: Results of a national study. JAMA. 1998;279(19):1548-53.
35. Pfeifer S. Alternative heilmethoden bei psychischen erkrankungen. Basel, SUISSE: Schwabe & amp Co; 1993.

36. Sabo CE, Michael SR, Temple LL. The use of alternative therapies by diabetes educators. The Diabetes Educator. 1999;25(6):945-56.
37. Pawa M. Complementary therapy use. In: Dunning T, editor. Complementary therapies and the management of diabetes and vascular disease. 1 ed. Cippenham, Wiltshire, Great Britain: John Wiley & Sons Ltd; 2006. p. 24-5.
38. Leese GP, Gill GV, Houghton GM. Prevalence of complementary medicine usage within a diabetes clinic. Practical Diabetes International. 1997;14(7):207-8.
39. Egede LE, Ye X, Zheng D, Silverstein MD. The prevalence and pattern of complementary and alternative medicine use in individuals with diabetes. Diabetes Care. 2002;25(2):324-9.
40. Dharma AD. Pengaruh latihan pasrah diri terhadap kontrol gula darah pada penderita diabetes melitus tipe 2 dengan gejala depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2006.
41. Petrak F, Herpertz S. Treatment of depression in diabetes: An update. Current Opinion in Psychiatry. 2009;22(2):211-7.
42. Markowitz S, Gonzalez JS, Wilkinson JL, Safren SA. Treating depression in diabetes: Emerging findings. Psychosomatics. 2011;52(1):1-18.
43. Stoop CH, Nefs G, Pommer AM, Pop VJM, Pouwer F. Effectiveness of a stepped care intervention for anxiety and depression in people with diabetes, asthma or copd in primary care: A randomized controlled trial. Journal of Affective Disorders. 2015;184:269-76.
44. Williams JJW, Katon W, Lin EHB, Noël PH, Worchel J, Cornell J, et al. The effectiveness of depression care management on diabetes-related outcomes in older patients. Annals of Internal Medicine. 2004;140(12):1015-24.
45. Katon WJ, Von Korff M, Lin EH, Simon G, Ludman E, Russo J, et al. The pathways study: A randomized trial of collaborative care in patients with diabetes and depression. Arch Gen Psychiatry. 2004;61.
46. Stiefel F, Zdrojewski C, Bel Hadj F, Boffa D, Dorogi Y, So A, et al. Effects of a multifaceted psychiatric intervention targeted for the complex medically ill: A randomized controlled trial. Psychotherapy and Psychosomatics. 2008;77(4):247-56.
47. Bogner HR, Morales KH, Post EP, Bruce ML. Diabetes, depression, and death. A randomized controlled trial of a depression treatment program for older adults based in primary care (PROSPECT). 2007;30(12):3005-10.
48. Gois C, Dias VV, Carmo I, Duarte R, Ferro A, Santos AL, et al. Treatment response in type 2 diabetes patients with major depression. Clinical Psychology & Psychotherapy. 2014;21(1):39-48.
49. Archer J, Bower P, Gilbody S, Lovell K, Richards D, Gask L, et al. Collaborative care for depression and anxiety problems. Cochrane database syst rev 2012.
50. Katon WJ, Lin EHB, Korff MV, Ciechanowski P, Ludman EJ, Young B, et al. Collaborative care for patients with depression and chronic illnesses. N Engl J Med. 2010;363.
51. Lamers F, Jonkers CCM, Bosma H, Knottnerus JA, van Eijk JTM. Treating depression in diabetes patients: Does a nurse-administered minimal psychological intervention affect diabetes-specific quality of life and glycaemic control? A randomized controlled trial. Journal of Advanced Nursing. 2011;67(4):788-99.
52. Mocking RJT, Assies J, Bot M, Jansen EHJM, Schene AH, Pouwer F. Biological effects of add-on eicosapentaenoic acid supplementation in diabetes mellitus and co-morbid depression: A randomized controlled trial. PLoS ONE. 2012;7(11):e49431.
53. Pibernik-Okanović M, Hermanns N, Ajduković D, Kos J, Prašek M, Šekerija M, et al. Does treatment of subsyndromal depression improve depression-related and diabetes-related outcomes? A randomised controlled comparison of psychoeducation, physical exercise and enhanced treatment as usual. Trials. 2015;16:305.
54. The Look ARG. Impact of intensive lifestyle intervention on depression and health-related quality of life in type 2 diabetes: The look ahead trial. Diabetes Care. 2014;37(6):1544-53.
55. Baumeister H, Nowoczin L, Lin J, Seifferth H, Seufert J, Laubner K, et al. Impact of an acceptance facilitating intervention on diabetes patients; 2019; acceptance of internet-based interventions for depression: A randomized

controlled trial. Diabetes Research and Clinical Practice.105(1):30-9.
56. Amsterdam JD, Shults J, Rutherford N, Schwartz S. Safety and efficacy of s-citalopram in patients with co-morbid major depression and diabetes mellitus. Neuropsychobiology. 2006;54(4):208-14.
57. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: A randomized double-blind placebo-controlled trial. Diabetes Care. 2000;23(5):618-23.
58. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomised placebo controlled 6-month trial. BMC Family Practice. 2007;8(1):1-7.
59. Lustman PJ, Clouse RE, Nix BD, et al. Sertraline for prevention of depression recurrence in diabetes mellitus: A randomized, double-blind, placebo-controlled trial. Archives of General Psychiatry. 2006;63(5):521-9.
60. Karaiskos D, Tzavellas E, Ilias I, Liappas I, Paparrigopoulos T. Agomelatine and sertraline for the treatment of depression in type 2 diabetes mellitus. International Journal of Clinical Practice. 2013;67(3):257-60.
61. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, et al. Effects of nortriptyline on depression and glycemic control in diabetes: Results of a double-blind, placebo-controlled trial. Psychosomatic Medicine. 1997;59(3):241-50.
62. Biagetti B, Corcoy R. Hypoglycemia associated with fluoxetine treatment in a patient with type 1 diabetes. World Journal of Clinical Cases : WJCC. 2013;1(5):169-71.
63. Goodnick PJ, Kumar A, Henry JH, Buki VM, Goldberg RB. Sertraline in coexisting major depression and diabetes mellitus. Psychopharmacol Bull. 1997;33.
64. Warnock JK, Biggs F. Nefazodone-induced hypoglycemia in a diabetic patient with major depression. The American Journal of Psychiatry. 1997;154(2):288-9.
65. Adnitt PI. Hypoglycemic action of monoamineoxidase inhibitors (maoi's). Diabetes. 1968;17(10):628-33.
66. Isotani H, Kameoka K. Hypoglycemia associated with maprotiline in a patient with type 1 diabetes. Diabetes Care. 1999;22(5):862-3.
67. Pollak PT, Mukherjee SD, Fraser AD. Sertraline-induced hypoglycemia. Annals of Pharmacotherapy. 2001;35(11):1371-4.
68. Lustman PJ, Williams MM, Sayuk GS, Nix BD, Clouse RE. Factors influencing glycemic control in type 2 diabetes during acute- and maintenance-phase treatment of major depressive disorder with bupropion. Diabetes Care. 2007;30(3):459-66.
69. Rubin RR, Ma Y, Marrero DG, Peyrot M, Barrett-Connor EL, Kahn SE, et al. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. Diabetes Care. 2008;31(3):420-6.
70. Rubin RR, Gaussoin SA, Peyrot M, DiLillo V, Miller K, Wadden TA, et al. Cardiovascular disease risk factors, depression symptoms and antidepressant medicine use in the look ahead (action for health in diabetes) clinical trial of weight loss in diabetes. Diabetologia. 2010;53(8):1581-9.
71. WHO. Who traditional medicine strategy 2002–2005. Geneva: WHO, 2002.
72. Vickers A. Massage and aromatherapy: A guide for health professionals. 1st ed. London: Chapman and Hall; 1996.
73. Ernst E, Rand JI, Stevinson C. Complementary therapies for depression: An overview. Archives of General Psychiatry. 1998;55(11):1026-32.
74. Stenström U, Göth A, Carlsson C, Andersson P-O. Stress management training as related to glycemic control and mood in adults with type 1 diabetes mellitus. Diabetes Research and Clinical Practice. 2003;60(3):147-52.
75. Surwit RS, van Tilburg MAL, Zucker N, McCaskill CC, Parekh P, Feinglos MN, et al. Stress management improves long-term glycemic control in type 2 diabetes. Diabetes Care. 2002;25(1):30-4.
76. Aviles JM, Whelan SE, Hernke DA, Williams BA, Kenny KE, O'Fallon WM, et al. Intercessory prayer and cardiovascular disease progression in a coronary care unit population: A randomized

controlled trial. Mayo Clinic Proceedings. 2001;76(12):1192-8.
77. Lorig KR, Ritter PL, Laurent DD, Fries JF. Long-term randomized controlled trials of tailored-print and small-group arthritis self-management interventions. Medical Care. 2004;42(4):346-54.
78. Muin N. Pengaruh latihan pasrah diri (lpd) ditambah fluoxetin dibanding fluoxetin terhadap penurunan kadar fruktosamin penderita pengidap diabetes melitus tipe 2 dengan simtom depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2015.
79. Rudiansyah M. Pengaruh latihan pasrah diri terhadap kadar c-reactive protein pada penderita diabetes mellitus tipe 2 dengan gejala depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2008.
80. Kusbandono S. Pengaruh kombinasi latihan pasrah diri dan fluoxetin dibandingkan dengan fluoxetin tunggal terhadap perubahan kadar high sensitivity c-reactive protein: Studi pada penderita diabetes melitus tipe 2 dengan simtom depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2015.
81. Widodo T. Pengaruh latihan pasrah diri terhadap angka lekosit pada penderita diabetes melitus tipe 2 dengan gejala depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2008.
82. Kurnianingrum NMA. Pengaruh kombinasi latihan pasrah diri dan fluoxetin dibandingkan dengan fluoxetin tunggal terhadap perubahan kadar endothelin-1 : Studi pada penderita diabetes melitus tipe 2 dengan simtom depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2015.
83. Sari W. Pengaruh kombinasi latihan pasrah diri dan fluoxetin dibandingkan dengan fluoxetin tunggal terhadap perubahan kadar oksida nitrit : Studi pada penderita diabetes melitus tipe 2 dengan simtom depresi. [Thesis]. In press 2016.
84. Novianto D. Pengaruh latihan pasrah diri terhadap kontrol tekanan darah penderita diabetes melitus tipe 2 dengan hipertensi dan gejala depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2006.
85. Hidayat N. Pengaruh latihan pasrah diri terhadap kualitas hidup pada penderita diabetes melitus tipe 2 dengan gejala depresi [Thesis]. Yogyakarta: Gadjah Mada University; 2008.
86. Astin JA, Shapiro SL, Eisenberg DM, Forys KL. Mind-body medicine: State of the science, implications for practice. The Journal of the American Board of Family Practice. 2003;16(2):131-47.
87. Zalaquett CP, McGraw A. Clinician's complete reference to complementary/alternative medicine. Novey D, editor. New York: Mosby; 2000. 114-29 p.