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Effect of self surrender practice on insulin resistance in individuals withtype 2 diabetes mellitus without depression: asingle-blinded randomized controlled trial

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ABSTRACT

Self surrender practice (*latihanpasrahdiri*/LPD) is a form of relaxation therapy that has been increasingly used, not only in the treatment of psychosomatic diseases, but also of other non-psychosomatic diseases. Previous studies reported thatSSP shows modest improvement on clinical parameters of type 2diabetes mellitus(T2DM) patients,not onlydepression symptoms improvement, but also glycemic control.However, the effect of LPD on insulin resistance has not been investigated. The study aimed to investigate the effect of LPD on insulin resistance in T2DM patients without depression. This was a single-blinded, randomized, controlledtrial conducted in outpatient unit of the Department of Internal Medicine, Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java.The subjects of the study were T2DM patients aged over 30 yearsand had no depression.Fourthy-four T2DM patients were randomized into two groups as the controlgroup and the treatment group who underwent SSP group for eight weeks. The data of insulin resistancemeasured by HOMA-IR, perceived stress scale (PSS), fasting plasma glucose (FBG), HbA1c, and two hour plasma glucose (PPG)levels of both groups werecollected and statistically analysed.No significantly different in the patient'scharacteristics of both groups was observed.At the end of the study period, the LPD group showed reduction of HOMA-IR and HbA1c but not statistically significant, (ΔHOMA-IR = -0.39±1.52; p = 0.976; HbA1c=-0.55±0.85%; p = 0.189). The FBG and PPGincreased in the LPD group compared to control but also not statistically significant (ΔFBG=10.16±50.33; p=0.294; PPG=40.74±69.35; p=0.062). We also observed the decrease of stress level in LPD group compared to control groupbut it was no statistical significance (ΔPSS=-5.09±6.47; p=0.655).Self surrender practice (LPD) decreasesHOMA-IR, improves glycemic control (HbA1c) and reduces stress levels in T2DM patients without depressionAlthough the theyarenot statisticallysignificant, however they may be clinically significant.

ABSTRAK

Latihan pasrah diri (LPD) adalah suatu bentuk terapi relaksasi yang makin banyak digunakan, tidak hanya untuk terapi penyakit psikosomatik, tetapi juga untuk penyakit non-psikosomatik. Beberapa peneliti sebelumnya membuktikan bahwa LPD terdapat perbaikan yang cukup pada parameter klinis pasien diabetes mellitus tipe 2 (DMT2). Latihan pasrah diri tidak hanya memperbaiki gejala depresi, tetapi juga kontrol glikemik. Namun demikian, masih belum diketahui apakah LPD juga mempengaruhi resistensi insulin. Penelitian ini bertujuan untuk mengkaji LPD terhadap resistensi insulin pasien DMT2 tanpa depresi. Penelitian ini merupakan studi buta tunggal, acak, terkontrol yang dilakukan selama 8 minggu pada pasien rawat jalan di Departemen Penyakit Dalam RSUP Dr. Soeradji Tirtonegoro, Klaten, Jawa Tengah. Subjek penelitian adalah pasien berusia lebih dari 30 tahun yang didiagnosis DMT2 dan tidak depresi. Sebanyak 44 pasien DMT2 dikelompokkan secara acak menjadi 2 kelompok, kelompok kontrol dan kelompok uji yang melakukan LPD selama delapan minggu. Data resistensi insulin yang diukur dengan HOMA-IR, *perceived stress scale* (PSS), glukosa plasma puasa (GPP), HbA1c, dan glukosa plasma 2 jam setelah makan (PPG) diukur dan di analisis secara statistik. Karakteristik

Keywords:
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HbA1c;
HOMA-IR;

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dasar antara kedua kelompok tidak berbeda secara bermakna. Pada akhir masa studi, kelompok LPD menunjukkan pengurangan HOMA-IR dan HbA1c tetapi tidak bermakna secara statistik, (ΔHOMA-IR=-0,39±1,52; p=0,976; HbA1c=-0,55±0,85%; p=0,189). Nilai GPP dan PPG meningkat pada kelompok LPD dibandingkan dengan kontrol tetapi tidak bermakna secara statistik (ΔFBG=10,16±50,33; p=0,294; PPG= 40,74±69,35; p=0,062). Kami juga mengamati berkurangnya tingkat stres pada kelompok LPD dibandingkan dengan kelompok kontrol meskipun tidak bermakna secara statistik (ΔPSS=-5,09±6,47; p=0,655). Latihan pasrah diri menurunkan HOMA-IR, meningkatkan kontrol glikemik (HbA1c) dan mengurangi tingkat stres pada pasien DMT2 tanpa depresi. Meskipun hasil tidak bermakna secara statistik, namun mungkin bermakna secara klinis.

INTRODUCTION

Insulin resistance is a prior condition that precedes type 2 diabetes mellitus (T2DM),[1] even it persists indefinitely after the diagnosis is established along with pancreatic β-cell dysfunction.[2,3] Treatment of T2DM aimedat improving insulin resistance has been proved to improve glycemic control,[4]thereby decreasing cardiovascular risk and mortality.[5]

Stress experienced by diabetic patients either because of the difficulty facing the disease or other life problems in a certain sense can affect conditions of insulin resistance that already exists.[6] Furthermore, it was proven that some anti-depressant drugs used in diabetics with depression may reduce insulin resistance,[7] but some other anti-depressant drugs actually exacerbate insulin resistance.[7-9] The effect of anti-depressant drugs on glycemic control that remain inconsistent dictate that the non-pharmacologic stress management has its place to receive attention.

Some alternative therapies such as yoga and certain stress management techniques have been proved to improve insulin resistance and glycemic control in diabetic patients,[10,11] but unfortunately, research on this is still very rare. The world of research is still unable to clearly answer the effectiveness of non-pharmacological therapy in improving insulin resistance in order to achieve good glycemic control.

Self surrender practice (SSP), in bahasa *latihan pasrah diri* (LPD), is a non-pharmacological stress management techniques that has been developed in UniversitasGadjah Mada, Yogyakarta. The ease of doing and simplicity make the LPD studied in more extent than never before, especially concerning its efficacy in depression. Because stress management is said to improve insulin resistance, the LPD as one of the stress management modalities should be tested to be applied among diabetic patients even without depression comorbid, in the hope of helping to improve insulin resistance and achieve better glycemic control. The goal is simply tocomplement the treatment of T2DMwith an easier, cost-effective way, while maintaining the standard therapy.

The research on the effectiveness of non-pharmacological therapy in improving insulin resistance is limited. However, through extensive literature tracking, some research on the effectiveness of yoga, herbal therapy, and dietary supplements in helping diabetic management avail to be obtained, although not directly associated with insulin resistance. Homeostatic model assessment – insulin resistance (HOMA- IR) is a method to assess pancreatic beta cell function and insulin resistance using basal (fasting) glucose and insulin concentrations. A study involving 90 subjects with polycystic ovary syndrome, showed yoga might improveinsulin resistance (HOMA-IR) in that population.[11] Another studies of physical and relaxation theraphy such as yoga and *Qigong* showed reduced stress level and might improves insulin

resistance.[12-20] Our hypothesis is the reduced stress level will decrease plasma cortisol level through hypothalamus-pituitary-adrenal (HPA) axis pathway and improve glycemic control and insulin resistance in diabetic patients. This study was conducted to investigate the effect of LPD on insulin resistance in T2DM without depression.

MATERIALS AND METHODS

Study design

This was a randomized, controlled, single-blinded in a single-center trialto evaluate the effects of eight weeks LPD on insulin resistance among T2DM patients without depression. The study was conducted in Out patient Unit of the Department of Internal Medicine, Dr. Soeradji Tirtonegoro General Hospital, Klaten, Central Java from December 2017 to January 2018 after an ethical approval was obtained from the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta and Dr. Soeradji Tirtonegoro General Hospital, Klaten. The T2DM were randomized 1:1 by random number generator. The sealed white envelope containing the serial number of the study was used for allocation concealment. Random allocation was conducted by third person. This studywas single-blinded because the assessor was blinded from knowing which subject receiving intervention or in the control group.

Population and Sample

Samples were obtained through consecutive sampling method. Each patient who fulfilled the inclusion and exclusion criteria was included in the study until the minimum sample size was achieved. The subjects were patients aged 30-60 years old who were diagnosed with T2DM and hadno depression as evidenced by Beck Depression Inventory [BDI] with score <17. The inclusion criteria in this research were out patients who are on medical record returned with diagnosis of T2DM (according to criteria of PERKENI 2015), moslems, aged 30-60 years, who checked themselves into the Internal Medicine Clinic, Dr. Soeradji Tirtonegoro General Hospital, Klaten, and agreed to follow the research by signing an informed consent.

The exclusion criteria in this research were patients who had BDI score of >17, were in treatment with anti-depressant drugs not due to depression indications (eg, neuropathy, neuralgia, epilepsy, protracted hiccup, etc.), are currently in psychotherapy, unable to follow the instructions and implementation of LPDs due to non-compliance (<80% adherence) and had disability or certain diseases (deaf, blind, illiterate, mental retardation, severe spinal deformities that reduce vital capacity of the lung, Alzheimer's disease, psychosis, moderate to severe chronic obstructive pulmonary disease, and class 3 to 4 chronic heartdisease), pregnant, smokers, active infections, autoimmune diseases, malignancy, chronic renal failure, and chronic liver disease. Screening of exclusion criteria was conducted through anamnesis, physical examination, and evaluating data on medical record.

Measurement

The parameter measured were stress level by perceived stress scale (PSS), insulin resistance (measured with HOMA-IR), fasting blood glucose (FBG), hemoglobinA1c (HbA1C), and 2-hours post prandial glucose (PPG). The depression was measured by Beck depression inventory (BDI) score (patient with BDI less than 17 were ruled out). Confounding variables were age, sex, and ethnicity,[21] diet, physical activity, adherence in carrying out LPDs, drugs being consumed, and comorbidities.

Confounding variables can be partially controlled by the restriction method.

Intervention

The LPD was conducted according to the method developed in the Psychosomatic Division, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta. The treatment was performed twice a day, each for 20min, and continued for eight weeks. The LPD was conducted by first the subject must willing to conducted the LPD then pray before the treatment, then inhaled slowly through both nostrils with mouth and eyes closed and did dhikr imagined the positive energy and positive feeling flowing inside the body, continued by holding breath for 15 sec, still did dhikr and imagine the positive energy was spreading all over the body and organs then exhaled slowly through the mouth while imagined all the hardship were going out the body along with the breath, take 1-2 regular breath and repeat the sequences. During the three days prior to the start of the intervention, the treatment group was trained to perform LPD techniques with guided practice on how to properly conduct LPDs so that they are competent and able to conduct their own LPDs at home on schedule, while filling out the LPD compliance sheet each time they did the LPD, after which a post test will be delivered (assessing the ability to memorize, to properly conduct LPDs, and to correctly measure the pulse for exercise zone).[22] During the study, patients in both groups continued to receive standard therapy (education, diabetes diet, oral anti hyperglycemic drugs and/or insulin). The LPD was not conducted during study period in control group, but for ethical reason, LPD was performed in control group after the study have finished. Side-effects that occurred due to the use of diabetes drugs and LPD are recorded and monitoring was carried out as well as medical intervention if necessary. In case of severe side effects, the LPD was stopped, and the subjects were advised to immediately contact the research team.

Patients were scheduled to visit the Internal Medicine Clinic of Dr. Soeradji Tirtonegoro General Hospital, Klaten prior to intervention for baseline data collection then at the fourthand eighth weeks for data collection. Evaluating compliance and remindingthe LPD procedures, and the insulin resistance check (HOMA-IR), PSS, FBG, HbA1c. HOMA-IR, PPG,and HbA1c that were performed at the Laboratory of Dr. Soeradji Tirtonegoro General Hospital, Klaten. Perceived stress scale were performed by patients in the Internal Medicine Clinic by filling out a validated Indonesian version of PSS questionnaire.[23] Compliance of subjects in performing LPD were assessed with attendance sheet given to the subjects in intervention group that required to be signed by subject and assessor each time.

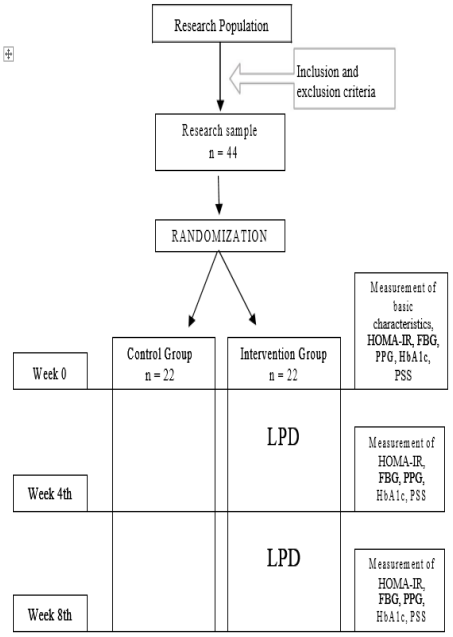

FIGURE 1.Research flow diagram

Outcomes

The primary outcome was insulin resistance (HOMA-IR). Secondary outcomes were HbA1c, FBG, and PSS. Primary and secondary outcomes were measured at the start of the research, at fourth and the end of the eighth week.

Statistical analysis

Determination of sample size was calculated by G*power program (version 3.1.9.2).[26] The treatment group was a non-depressed T2DM patients who would undergo LPD for 8 weeks. The control group was a non-depressed T2DM patients who did not receive an LPD but at the end of the study would obtain an 8-week of LPD. An estimate of 22 sample in each group was considered sufficient to detect the effect of LPD on insulin resistance and glycemic control with powerof80%.

The basic characteristics of patients in both groups were presented in the form of mean and standard deviation or percentage. Differences in demographic data and clinical characteristics were analyzed by Chi-square test, independent ttest, Fisher exact test, or Mann-whitney test. The effect of LPD on insulin resistance (HOMA-IR) and glycemic control (HbA1c, FBG, and PPG) wereanalyzed using bivariate non-parametric Mann-Whitney test. The relationship between variables was considered significant if p <0.05 with 95% confidence interval.[21]

RESULTS

A total of 44 patients were randomized with 22 patients in control group and 22 patients in the treatment group. In the treatment group male were 9 and female were 13 while in the control group male were 9 and female were 13 patients. No significantly difference in gender, age, insulin used, hypertention, microvascular and macrovascular complication, nutritional status, blood pressure, FBG, PPG, HbA1C, HOMA-IR, and PSS as well as duration of DM between the two groups was observed (p>0.05) (TABLE 1).

TABLE 1. Basic characteristics of research subjects

Variable	Intervention (n=22) n (%)	Control (n=22) n (%)	p
Sex			
• Man	9(40.9)	9 (40.9)	1.00
• Woman	13(59.1)	13(59.1)	
Age (mean±SD years)	55.27 ± 7.18	54.41 ± 5.08	0.648[b]
Duration of DM (years)	7.18 ± 5.67	6.31 ± 5.76	0.399[d]
Drug			
• With insulin	12 (54.55)	10 (45.45)	0.763[a]
• Without insulin	10 (45.45)	12 (54.55)	
Comorbit (hypertension)	7 (31.8)	7 (31.8)	1.00
Complication			
• Microvaskuler	17 (77.27)	13 (59.09)	0.332[a]
• Macrovaskuler	2 (9.09)	0 (0)	0.488[c]
Nutritional status			

• Normoweight	7 (31.8)	4 (18.18)	
• Overweight	10 (45.54)	8 (36.36)	0.258[a]
• Obese	5 (22.72)	10 (45.54)	
Blood pressure			
• Systolic (mean+SD mmHg)	129.09 ± 18.74	126.59 ± 14.91	0.720[b]
• Diastolic (mean+SD mmHg)	76.90 ± 8.68	76.81 ± 5.01	0.680[b]
FBG (mean+SD mg/dL)	154.64 ± 44.24	158.77 ± 76.18	0.827[b]
PPG (mean+SD mg/dL)	276.82+70.18	271.45+104.99	0.081[b]
HbA1c (%) (mean+SD%)	9.19 ± 1.72	8.26 ± 2.26	0.893[b]
HOMA-IR (mean+SD)	6.45+9.11	15.19+24.13	0.131[b]
PSS (mean+SD)	15.03 ± 19.31	17.09 ±6.22	0.155[b]

Legends : [a]Chi-square test[b];Independent ttest; [c]Fisher exact test[d]; Mann-whitney test; FBG: fasting plasma glucose; PPG: 2-hours plasma glucose; HOMA-IR: homeostasis of model assessment insulin resistance; PSS: perceived stress scale

HOMA-IR was observed to change overtime in both groups. The mean of HOMA-IR in the intervention group obtained at the beginning of the study was 3.33±3.85 and at the end of 8th weeks it decreasedto 2.94±4.21 (FIGURE 2). In the control group, the HOMA-IR at the beginning of treatment was 4.83± 4.54 and the end of 8th weeks it increased to 5.08± 5.56. In the intervention group, there was a decrease of HOMA-IR at the end of intervention of 0.39± 1.52 while in the control group increased by 0.25 ± 2.60(p= 0.976). Multivariate analysis of HOMA-IR to age, gender, and was performed but we found no statistically significant relationship (p>0.05).

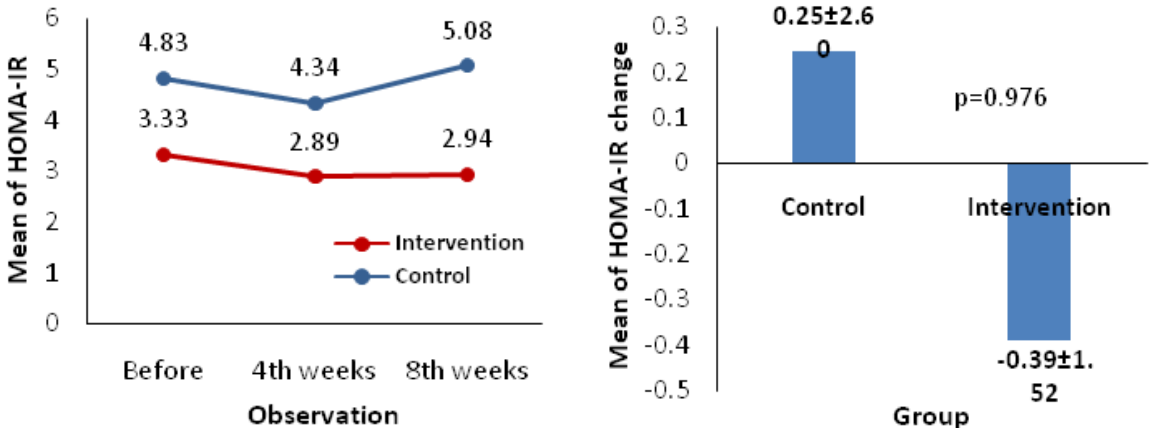

FIGURE 2. HOMA-IR changes after intervention

PSS was also changed in both of the groups (FIGURE 3). The mean of PSS in the intervention group obtained at the beginning of the research was 15.36 ± 5.12 and there was a decrease in 1-month and 2-months treatment of 13.59 ± 5.08 and 10.27 ± 6.49 respectively. In the control group the mean of PSS at the beginning of treatment was 17.09 ± 6.22, at the end of 4th weeks 16.36 ± 5.86 and at the end of 8th weeks 12.45 ± 4.68. In the treatment group, the decrease of PSS at the end of intervention was 5.09 ± 6.47 while in the control group decreased by 4.64 ± 5.21 (p= 0.655).

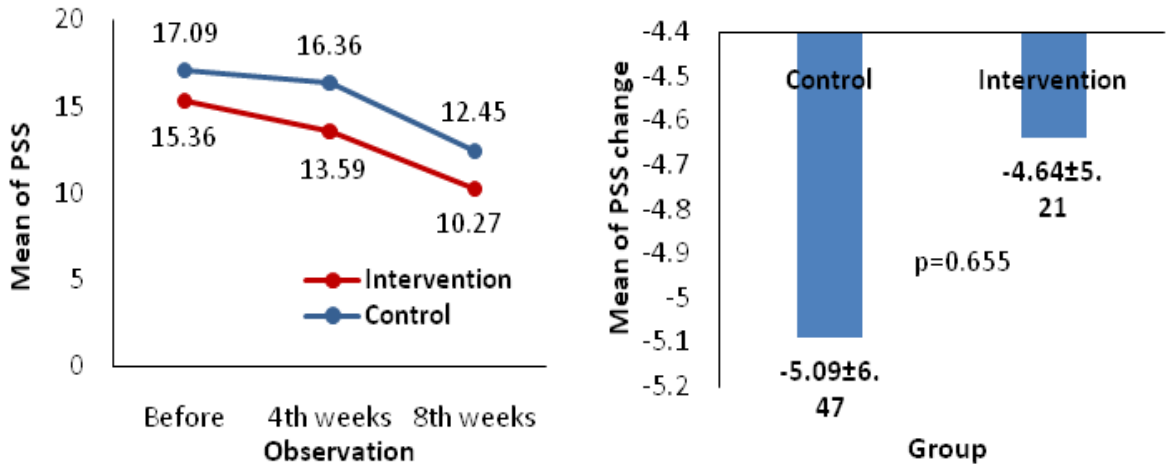

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FIGURE 3. PSS changes after intervention

The average of HbA1c in the intervention group obtained at the beginning of the study was 9.03± 1.74% and 8.48 ±1.78% at the end of 8th weeks (FIGURE 4). In the control group the average of HbA1c at the beginning of the intervention was 8.34± 1.76% and increased by the end of the eight weeks of treatment 8.48± 1.78%. In the treatment group, HbA1c decreased at the end of the intervention by -0.55± 0.85% while in the control group decreased by -0.13± 0.82% (p= 0.189).

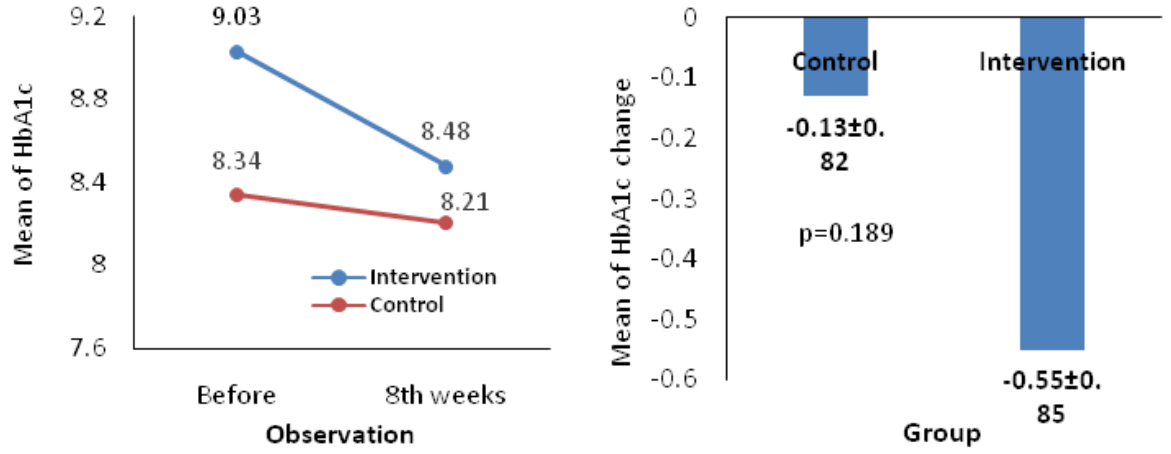

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FIGURE 4. HbA1c changes after intervention

The average of FBG in the intervention group obtained at the beginning of the research was154.63± 44.24 mg/dl and there was an increase in the end of fourth weeks of treatment 169.05± 55.22 mg/dL and at the end of treatment 174.81± 81.68 mg/dL (FIGURE 5). In the control group the mean of FBG at the beginning of study was 158.77± 76.18 mg/dL increased at the end of fourth weeks 158.77± 62.16 mg/dL and at the end of the study theFBGwas 144.59±45.74 mg/dL. In the treatment group, there was an increase of FBG at the end of intervention of 20.18± 65.34 mg/dL while in the control group was a decrease by -14.18± 65.44 mg/dL(p = 0.296).

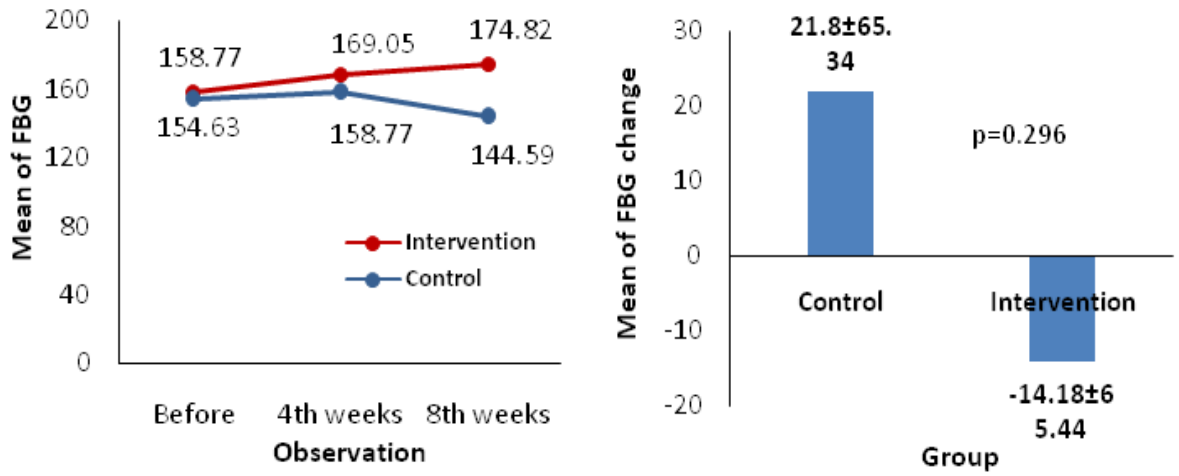

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FIGURE 5. FBG changes after intervention

The average of PPG in the treatment group subjects obtained at the beginning of the research was163.82±70.18 mg/dL and there was an increase at the end of fourth weeks 291.27±82.11 mg/dL and at the end of second month 314.41±88.67 mg/dL (FIGURE 6). In the control group the mean of PPG at the beginning of treatment was 271.45±104.99 mg/dL, at the end of fourth weeks 282.32±115.73 mg/dL and at the end of study it was 267.82±83.99 mg/dL. In the treatment group, the increase of PPG at the end of intervention was 46.59±80.32 mg/dl while in the control there was a decrease of-3.64± 70.65 mg/dL(p=0.084).

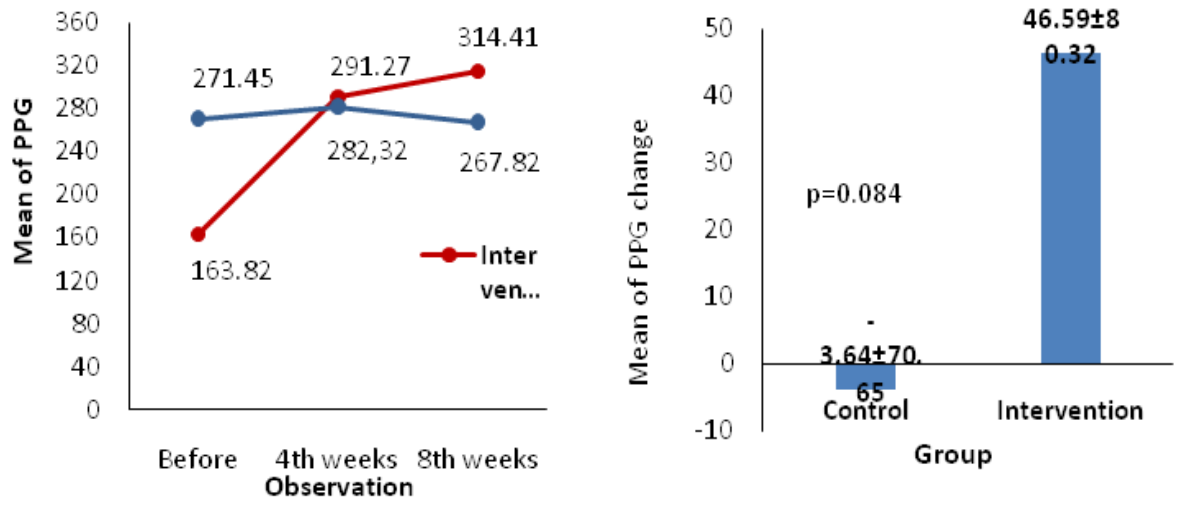

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FIGURE 6. Two hours of PPG levels changes after intervention

DISCUSSION

LPD is a non-pharmacologic stress management technique consist of breathing exercise, repetitive prayer and guided imagery and originally intended to treat depression and or non-psychotic anxiety that are common in patients with chronic physical illness. Several studies show some improvement of blood glucose levels, depression symptoms, and inflammatory markers in diabetic patients with depression.[27-30]

This study showed that LPD

improved glycemic control and insulin resistance in diabetic patients without depression although the improvement of HbA1C and HOMA-IR not statistically significant between the treatment and control groups. A study involving large subjects showed that decreasing HbA1c levels was associated with reduced mortality risk, particularly all-cause mortality.[31] The decrease in HbA1c achieved through this LPD was -0.55%. Data from UK Prospective Diabetes Study (UKPDS) which linked HbA1C reduction and diabetes-related complication showed that decrease in HbA1c by 1% reduced diabetes-related death by 21%, myocardial infarction by 14% and microvascular complication by 37%.[31-33] The mean decrease of HbA1c levels in the intervention group was -0.55%. It was equivalent to the decrease in HbA1c levels obtained by administration of α-glucosidase inhibitors (0.5–0.8%), DPP4 inhibitors (~ 0.5%), or GLP-1 agonists (~ 0.5%).[32] The improvement of insulin resistance and glycemic control were not statistically significant, however, the result might be clinically significant and might be able to paving the way for LPD to play role in T2DM management even if depression is not present. Our study showed longer duration ofT2DM in intervention compared to control group (7.18±5.67 years vs 6.31±5.67 years respectively; p=0.399).Although they were not statistically significant, it might blunted the effect of LPD towards improvement of the HOMA-IR and HbA1c in intervention group.

The exact mechanism how LPD improves insulin resistance and glycemic control remain unknown. This effect might be mediated through stress reduction that affected the hypothalamus-pituitary axis (HPA) that resulted in decreasing cortisol level, improving insulin resistance and glycemic control.

This study showed increased FBG and PPG at the end of study but not statistically significant. This contradicted the result that observed a decrease in HbA1c, indicating that there should also be a decrease in both FBG and PPG levels. It was said that PPGwas correlated to HbA1c more than FBG,[34] but in this research, the correlation was not seen. This was due to the possible length of the research that was not long enough, considering the HbA1c represent the stability of blood sugar in ± 3 months, while this research lasted only 2 months. However, it cannot be concluded that LPDs caused dysregulation of glycemic control. Previous research had even shown an opposite results.[27] Longer follow-up is required to clarify this condition.

Unlike HbA1c, it is not known whether a decrease in insulin resistance characterized by HOMA-IR decline can provide clinical benefit. Insulin resistance is associated with abnormalities in various organs, including polycystic ovary syndrome, cancer, infection, obesity, andT2DM.[35,36] Insulin resistance is also associated with conditions of hypertension, hyperglycemia, and dyslipidemia.[1,37] In non-diabetic patients, healthy subjects and other patients of chronic diseases, increased HOMA-IR denote increasing risk factors for death and cardiovascular incidence.[38-41] In the condition of diabetes itself, insulin resistance plays a role in glucotoxicity that occurs in line with the decreased function of pancreatic β cells.[3]

Studies on relaxation therapy in diabetics reported a decrease in HOMA-IR, along with stress or depression symptoms reduction, although the clinical benefit of the decline cannot be determined.[6,10,42,43] Research on the effectiveness of yoga in improving insulin resistance was done by Sahay,[12] involving only 5 subjects, in which the measurement of insulin resistance was not performed directly by calculating HOMA-IR.Several other researches using yoga to improve insulin resistance

have used HOMA-IR as an outcome and showed a decline in HOMA-IR although largely not statistically significant.[13-15] Correspondingly, Qigong relaxation exercises by Sun *et al.*[16] performed in patients with T2DM also showed HOMA-IR improvement although still not significant, but improvement of fasting glucose and HbA1c can be achieved significantly. A study conducted by Nidhi *et al.*[11] which involving 90 subjects with polycystic ovary syndrome, showed an improvement in insulin resistance (HOMA-IR) through the practice of yoga for 1 h per day for 12 weeks. Our study showed similar result that the intervention group had lower value of HOMA-IRbut not statistically significant. However, our research remains important because it was the first study to describe the effect of LPD on insulin resistance directly.

This study showed that in the intervention group there was a greater decrease of PSS than the control group, although it was not statistically significant. The limitation of this study was small sample size and short duration of the intervention (8 weeks of LPD). For future research, a larger study with more severe T2DM participant and LPD with longer duration may be needed to achieved a significant treatment effect.

CONCLUSION

Self surrender practice (*latihan pasrah diri*/LPD) decreases HOMA-IR, improves glycemic control (HbA1c) and reduces stress levels in diabetic patients without depression.Although it was not significantly different, however it may be clinically significant.

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