

Review Article:

ADEQUATE MANAGEMENT OF DEPRESSION AND NEUROPATHIC PAIN IN PATIENT WITH TYPE 2 DIABETES

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ABSTRAK

Diabetes dan depresi merupakan gangguan kesehatan yang paling serius di masyarakat. Depresi pada pasien dengan diabetes tipe 2 berhubungan dengan kepatuhan pengobatan yang buruk, gangguan kualitas hidup, peningkatan hiperglikemia, komplikasi diabetes lainnya, dan kematian. Depresi berhubungan dengan nyeri neuropatik tersambung. Sejumlah penelitian telah mendokumentasikan efektivitas pendekatan pengobatan konvensional seperti farmakoterapi, terapi perilaku kognitif (CBT) dan olahraga pada pengelolaan depresi dan neuropatik pada pasien dengan diabetes tipe 2. Artikel ini membahas cara-cara untuk mengelola depresi dan nyeri neuropatik yang memadai pada pasien dengan diabetes tipe 2.

ABSTRACT

Diabetes and depression is one of the most serious medical disorders in public health. Depression in patients with type 2 diabetes is associated with poor treatment compliance, compromised quality of life, increased rates of hyperglycemia, other complications of diabetes, and mortality. Depression and neuropathic pain is connected. A number of studies have documented the efficacy of conventional treatment approaches such as pharmacotherapy, cognitive behavioral therapy (CBT) and exercise on managing depression and neuropathic in patients with type 2 diabetes. This article discussed ways to manage depression and neuropathic pain adequately in patient with type 2 diabetes.

Keywords : *Diabetes, Depression, Neuropathic Pain, Pharmacotherapy, CBT and Exercise*

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INTRODUCTION

Diabetes is a world problem of elderly health (Wild et al, 2004). It is “a silent killer” because of its no sign complications, serious chronic disease that leads to a substantial reduction in life expectancy, decreased quality of life, and increased costs of care. In 2010, Indonesia (Supari, 2005), one of a developing country, is predicted has 5 million cases diabetes, from 220 million citizens, and 75% occurs in productive age, around 40-45 years old. Thus, there are huge problems in all human aspect, such economic, social life, due to diabetes.

Patients with diabetes have been found to be two times more likely to experience depressive symptoms than their peers without diabetes. Rates of elevated depressive symptoms have been found to range from 21 to 27% in type 1 diabetes and type 2 diabetes. Although depression was detected in diabetic patients, sometimes it managed inadequately, only 33% of depression cases among diabetic patients are diagnosed and treated (Anderson et al., 2001). Moreover, patients with

diabètes, 30% have been found to suffer from chronic neuropathic diabetes. Due to large inter-subject variability in symptoms and in the absence of established diagnostic criteria, it is not surprising that diabetic neuropathic pain is under-reported and under-treated (Herman, 2005; Daousi, 2004). In the management of this condition it is important to discriminate between the treatment of pain and the treatment of neuropathy. Several unmet clinical needs relating specifically to assessment and management warrant urgent attention.

Depression is one of the most serious medical disorders in public health. Depression in patients with diabetes is associated with poor treatment compliance, compromised quality of life, increased rates of hyperglycemia, other complications of diabetes, and mortality (Ciechanowski et al., 2000; Lin et al., 2004; Katon et al., 2005). Whilst the clinical correlates of depression in patients with type 2 diabetes are well characterized, the neurobiological underpinnings of depression in these patients remain largely unknown.

Depression in Diabetes

The etiology of depression had not been precisely known yet, probably it was multi-factorial, including biological, genetic and psychosocial factors. Several neurotransmitters thought to be involved, including the dopamine, serotonin, adrenaline, GABA, and Second Messenger; also the role of the hypothalamic-pituitary-adrenal (HPA) axis, and thyroid glands. Some experts demonstrated that depression in patient with diabetes are associated with (1) lower concentrations of glutamate/glutamine, (2) deficit in function or amount of trimonoamines in neurotransmitters system (Norepinephrine, Serotonin and Dopamine), and (3) higher counter-regulator hormones (ACTH, Cortisol) of hypoglycemic effects of Insulin and alterations in glucose transporter. Nowadays, trimonoamine neurotransmitters were more understood as secondary or epiphenomenal effects, and the trend nowadays had shifted to the distal events, such as receptors or genetic / DNA systems. The abnormalities was also been found in the caudate nucleus, this may provide the subcortical component to abnormalities in pre-frontal subcortical circuits that mediate abnormalities in mood, cognition, and behavior. Preclinical models that target the caudate and other components of the circuit may help in further clarifying the anatomical and physiological correlates of depression in patients with type 2 diabetes (Kumar et al. 2009).

Depression and neuropathic pain in patients with diabetes

Depression can be also induced by neuropathic pain, due to the neurotransmitter that alleviate depression and pain such GABA (gamma amino butyric acid), Serotonin, Nor-epinephrine and Endorphine. Management of chronic neuropathic pain is a broad, holistic approach to management is generally considered essential. People with diabetes often feel misunderstood because there are no obvious signs of pain. Listening to and supporting these people, particularly those with severe pain, can in itself be therapeutic. Educating them about pain mechanisms can help to allay fears about undiagnosed disease or amputation. People with diabetes should also be informed about the benefits and limitations of treatment, and should be made aware that treatment is likely to achieve less than complete pain relief. Management of the chronic neuropathic pain should encompass lifestyle intervention, glycaemic control and pharmacological therapy for pain relief. In addition, risk factors for macrovascular disease, specifically hypertension, dyslipidaemia, obesity and smoking, should be managed effectively. There is also a need to assess and treat comorbidities, in particular depression, anxiety and

insomnia, which are common in people with diabetes who suffer from chronic neuropathic pain and influence pain perception

Early diagnosis of depression in patients with diabetes

According to DSM-IV criteria, symptoms of depression are depressed mood thus experience a loss of energy and interest, anhedonia feelings of guilt, difficulty in concentrating, loss of appetite, and thoughts of death or suicide. Other signs and symptoms of mood disorders include change in activity level, cognitive abilities, speech, and vegetative functions – e.g. sleep, appetite, sexual activity, and other biological rhythms – (Kanner, 2005; Sadock, 2007). These disorders virtually always result in impaired interpersonal, social, and occupational functioning. Hamilton Rating Scale for Depression might be used for physicians as a tool to determine depression in patients with diabetes.

Early diagnosis of neuropathic pain in patients with diabetes

Neuropathic pain is defined by the International Association for the Study of Pain as ‘pain initiated or caused by a primary lesion or dysfunction in the nervous system’ (Merskey H, 1994). Neuropathic pain can be detected using standardized scales for pain assessment, such as : 1) Short Form McGill Pain Questionnaire (SF-MPQ), 2) visual analog scale (VAS), 3) numeric rating Pain Disability Index and faces scales, 4) Pain Catastrophizing Scale (PCS) and 4) Neuropathic Pain Scale (NPS). One of the most widely used current evaluations is the 0-10 rating where “0” means “I have no pain” and “10” is “the worst pain I ever had. In all types of neuropathic pain there is a combination of sensory loss, giving rise to negative signs, and pain, causing a variety of positive symptoms and signs (Jensen, 2003). Pain may include dysaesthesia, an abnormal, unpleasant and disagreeable but not painful sensation (e.g. tingling), or allodynia, which is pain caused by a normal non-painful stimulus such as touch, or warm or cool temperatures. Hyperpathia also occurs. This is a phenomenon in which patients initially have an increased threshold to a stimulus because of their loss of afferent input but this is followed by an increased stimulus response, where patients suddenly perceive an explosion of pain. The extent of this condition is unclear. Quite often, patients experience more than one type of pain at the same time. Neuropathic pain can be categorized as spontaneous (continuous or intermittent) or provoked. Provoked pain can be further categorized as hyperalgesia (i.e. an exaggeration of the pain experienced in response to a noxious or painful stimulus).

Table 1. Symptoms and signs associated with diabetic neuropathy pain (Jensen, 2006)

Positive Symptoms and Signs	Negative Signs (i.e Deficits)
<ul style="list-style-type: none"> • Persistent distal burning or dull pain in feet • Persistent proximal aching pain in legs • Paroxysmal electric, shooting, stabbing pain • Dysaesthesias (painful paraesthesia) • Evoked pain (hyperalgesia, allodynia) 	<ul style="list-style-type: none"> • Hypoalgesia, analgesia • Hypoaesthesia, anaesthesia • Decrease in thermal, vibration and pressure sensation, abolition of reflexes

Provoked pain can also be categorized by the type of eliciting modality (i.e. mechanical, thermal or chemical) and by the way in which the stimulus is applied (whether a static, dynamic or stretch stimulus). This classification may assist categorisation into some of the underlying mechanisms of the pain itself.

Description of the symptoms and signs of diabetic neuropathy pain

Allodynia means pain due to nonnoxious stimuli (clothing, light touch) when applied to the affected area. May bemechanical (eg, caused by light pressure), dynamic (caused by nonpainful movement of a stimulus), or thermal (caused by nonpainful warm, or cool stimulus). Anaesthesia means Loss of normal sensation to the affected region. Hyperalgesia means exaggerated response to a mildly noxious stimulus applied to the affected region. Hypoalgesia means reduction of normal sensation to the affected region. Paraesthesia means nonpainful spontaneous abnormal sensations.

Pharmacotherapy. Management of depression and neuropathic pain in diabetes mellitus

There are classes of drugs that can be used in the management of depression and neuropathic pain in diabetes. Firstly, Selective Serotonin Reuptake Inhibitors (SSRI) - Sertraline is indicated for the treatment of major depressive disorder (MDD) and neuropathic pain in patients with diabetes, due to the inhibition of serotonin and norepinephrine reuptake. Maintenance therapy with sertraline prolongs the depression-free interval following recovery from major depression, and this condition was associated with improvements in glycosylated hemoglobin (HbA1C) levels (Lutsman et al., 2006). Secondly, $\alpha 2\delta$ ligands (Pregabalin, Gabapentin) is used to modulate voltage-gated calcium channels (Galluzzi, 2007). Thirdly, Tricyclic antidepressants (Amitriptylline) is used to inhibit serotonin and norepinephrine reuptake. Fourthly,

Opioid, the most powerful analgesia that works in blocking μ receptors.

Cognitive behavioral therapy (CBT)

CBT is a psychotherapeutic approach that aims to teach the person new skills, on how to solve problems concerning dysfunctional emotions, behaviors and cognitions through a goal-oriented, systematic procedure. There is empirical evidence that CBT is effective for the treatment of a variety of problems, including mood, anxiety, personality, eating, substance abuse, and psychotic disorders (Beck, 1993; Groot et al., 2010).

Physical activities or exercise

Physical activities or exercise recommended in patients with diabetes are aerobic exercise or 'regular moderate exercise' for 30 minutes a day for 5 days a week (Nagi, 2005). Exercise has benefit in diabetes therapy and it is based on the premise that raising tissue oxygen levels will enhance glucose metabolism via higher activation of glucose transporter and nitric oxide synthase. Exercise stimulates sympathetic nerves, then about 80–85 per cent of the cells secrete adrenaline directly into the blood stream, whilst the remaining 15–20 per cent secrete noradrenaline, that has effect in mood stabilizing. The circulating blood carries both neurotransmitters to the coronary blood vessels, reinforcing the sympathetic activity in the myocardium. This two-pronged approach produces two responses – an increased heart rate and a more forceful ventricular ejection. Thus, cardiac output is raised not only by faster beats but also by greater stroke volumes. The sympathetic division provides an important defense and survival mechanism. When attacked we can either stand and fight or turn and flee; the sympathetic division prepares us for both possibilities. Our heart rate increases immediately and rapidly; ventricles contract more strongly and raise blood pressure; blood is diverted from the skin and the gut to the muscle bed and

we become pale; our airways dilate ensuring greater lung ventilation; insulin secretion moves glucose from the blood into the muscle cells. Exercise increases Norepinephrine, one of monoamines in neurotransmitter that involved in mood stabilizing. Nowadays, It beliefs that exercise, as an accessible treatment strategy and in conjunction with traditional treatment approaches, may prove effective in providing synergistic effects on both depression and diabetes.

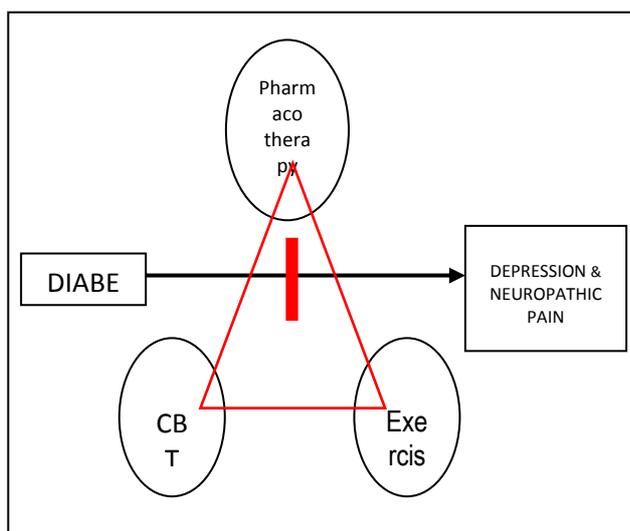


Figure 1. Schematic representation of a central role for managing depression and neuropathic pain in patients with diabetes

Pharmacotherapy, CBT and Exercise can prevent depression in diabetes

There is clearly an urgent need for exploring the use of interdisciplinary approach to prevent depression in people with type 2 diabetes, thus they will have better quality of life. Nowadays, only few researches, most in community, are done by combining pharmacotherapy and CBT, or pharmacotherapy and exercise, or CBT and exercise for people with diabetes. On the other hand, combination therapy of pharmacotherapy, CBT and exercise, also the information about biological change of the effect of these therapeutic combination is still rare. These combination are still widely opened to be studied.

REFERENCES

1. Anderson RJ, Freedland K, Clouse R, Lustman PJ (2001). The prevalence of comorbid depression in adults with diabetes: a meta-analysis. *Diabetes Care* 24:1069–1078

2. Beck A (1993). *Cognitive Therapy and the Emotional Disorders*. NY: Penguin : 978-989
3. Ciechanowski PS, Katon WJ, Russo JE (2000). Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 160(21):3278-3285
4. Daousi C, MacFarlane IA, Woodward A et al. (2004). Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes. *Diabet Med*;21:976-82.
5. Galluzzi KE (2007). Managing Neuropathic Pain, *JAOA : Supplement 6 : Nov : Vol 107 : No 11 : 39-49*
6. Groot M, Kushnick M, Doyle T, Merrill J, McGlynn M, Shubrook J, Schwartz F (2010). A Model of Community-Based Behavioral Intervention for Depression in Diabetes: Program ACTIVE, *Diabetes Spectrum* Volume 23, Number 1:18-25
7. Herman WH, Kennedy L (2005). Underdiagnosis of peripheral neuropathy in type 2 diabetes. *Diabetes Care*;28:1480-1.
8. Jensen TS, Baron R (2003). Translation of symptoms and signs into mechanisms in neuropathic pain. *Pain* 102:1-8
9. Jensen TS et al. (2006), New perspectives on the management of diabetic peripheral neuropathic pain, *Diab Vasc Dis Res*; 3; 108-121
10. Kanner AM (2005). Depression in Neurological Disorder, *Lunbeck Institute, Illionis :1-3*
11. Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, Kinder L, Young B, Von Korff M (2005). The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 28(11):2668-2672
12. Kumar A, Gupta R, Thomas A, Ajilore O, Helleman G (2009). *Arch Gen Psychiatry*. Vol. 66 (No. 3):324-330
13. Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, Ciechanowski P, Ludman EJ, Bush T, Young B (2004). Relationship of depression and diabetes selfcare, medication adherence, and preventive care. *Diabetes Care* 27(9): 2154-2160
14. Lustman PJ, Clouse RE, Nix BD, Freedland KE, Rubin EH, McGill JB, Williams MM, Gelenberg AJ, Ciechanowski PS, Hirsch IB (2006). Sertraline for Prevention of Depression Recurrence in Diabetes Mellitus : A Randomized, Double-blind, Placebo-Controlled Trial, *Arch. Gen. Psychiatry* Vol 63: 321-329
15. Merskey H, Bogduk N (eds). (1994). *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy*. Seattle: IASP Press, pp.209-14

16. Nagi D (2005). Exercise and Sport in Diabetes : 2nd Edition, John Wiley & Sons Ltd, England : 78-89
17. Sadock BJ, Sadock VA (2007). Mood Disorders : Kaplan & Sadock's Synopsis of Psychiatry : Behavioral Sciences / Clinical Psychiatry, 10th Ed., Lippincott Williams & Wilkins, Philadelphia USA, 15: 528-562
18. Supari SF (2005). In opening of Interactive symposium : "Diabetes? Don't be afraid of", June 8th, Jakarta. Available from www.depkes.go.id access on July 7th, 2009.
19. Wild S, Roglic G, Green A, Sicree R, King H (2004). Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053.