Gender Differences and White Blood Cells on Anxiety Symptoms in Type 2 Diabetes Mellitus: A Community-Based Study

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ABSTRACT

Gender differences and type 2 diabetes mellitus (T2DM)-associated inflammatory biomarkers are correlated with high levels of anxiety. However, no study has investigated gender differences and high level of white blood cells (WBC) on anxiety among participants with T2DM in Indonesia. We examined the roles of gender and WBCs on anxiety symptoms in T2DM. Cross-sectional study was performed on 294 patients with T2DM recruited from five community clinics with multistage cluster sampling. Depression, anxiety and Stress-21 (DASS-21) a standardized questionnaire was used to measure anxiety and WBCs was determined using an XP-100 automated hematology analyzer. The adjusted coefficients beta (coef. β) and 95% confidence interval (CI) were performed using multiple linear regression model. Statistical analyses were calculated using SPSS version 25.0, with a p value of <0.05 set as statistically significant. Famales exhibited significantly higher levels of anxiety (β=0.26, 95% CI=0.07–0.94) than male respondents. Notably, respondents with WBCs of $\geq$7.576 had significantly higher anxiety (β=2.04, 95% CI=1.12–3.71) than patients with WBCs of <7.576. There was high prevalence of axienty symptoms in this Indonesian sample of respondents. Female and high level of WBCs exist on increasing susceptibility to anxiety symptoms among individuals with T2DM.

ABSTRAK

Perbedaan jenis kelamin dan biomarker inflamasi terkait diabetes mellitus tipe 2 (T2DM) berkorelasi dengan tingkat kecemasan yang tinggi. Namun, belum ada penelitian yang menyelidiki perbedaan jenis kelamin dan sel darah putih (WBC) pada kecemasan di antara penyandang T2DM di Indonesia. Kami memeriksa peran jenis kelamin dan WBCs pada gejala kecemasan untuk penyandang T2DM. Studi cross-sectional dilakukan pada 294 penyandang T2DM yang diperoleh dari lima klinik komunitas dengan multistage cluster sampling. Depresi, Anxiety and Stress-21 (DASS-21) merupakan kusioner standar yang digunakan untuk mengukur kecemasan dan WBCs ditentukan dengan menggunakan penganalisis hematologi otomatis XP-100. Koefisien yang disesuaikan beta (koefisien β) dan interval kepercayaan 95% (CI) dilakukan dengan menggunakan model regresi linier berganda. Analisis statistik dihitung menggunakan SPSS versi 25.0, dengan nilai p <0.05 ditetapkan sebagai signifikan secara statistik. Wanita menunjukkan tingkat kecemasan yang jauh lebih tinggi (β = 0,26, 95% CI = 0,07-0,94) dibandingkan responden laki-laki. Khususnya, responden dengan

nilai WBCs ≥7.576 memiliki kecemasan yang lebih tinggi secara signifikan (β = 2.04, CI 95% = 1.12–3.71) dibandingkan responden dengan nilai WBCs <7.576. Terdapat prevalensi gejala axienty yang tinggi pada sample dari responden sampel di Indonesia dalam penelitian ini. Wanita dan nilai WBCs yang lebih tinngi memiliki peningkatan kerentanan terhadap gejala kecemasan di antara individu dengan T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a system of interconnected metabolic disorders characterized by escalated blood glucose concentration (American Diabetes, 2018). Patients with T2DM present a significantly increased risk of mortality compared to the general population (Ogurtsova et al., 2017), and T2DM is the most prevalent health problem on a major global scale (Saeedi et al., 2019). Interstingly, the International Diabetes Federation has estimated that the prevalence of individual with T2DM among Indonesian population will escalate from 10.7 million in 2019 to 16.6 million in 2045 (Saeedi et al., 2019). The rapidly increasing incidence of T2DM necessarily requires a deeper understanding of the factors that contribute to the disease's burden (Rias, Gordon, et al., 2020; Rias, Kurniawan, et al., 2020). Consequently, these determinant factors, which include demographic characteristics and inflammation markers may contribute the physcological factors such as anxiety symptoms of patients with the disease (Fazelian et al., 2019; Palizgir et al., 2013).

Anxiety symptoms commonly exist and affect individulas with T2DM (Liu et al., 2020; Rias, Gordon, et al., 2020). Few attempts have been made to rigorously research the correlettion between anxiety and hyperglycemia but often remain unrecognized in diabetes care program (Liu et al., 2020). Epidemiological evidence revealed that at least twice of individulas among T2DM suffer from clinically relevant anxiety disorders (Bouwman et al., 2010). Anxiety can influences how individuals perceive their objective health status and may have an effect on the incidence of diabetes by resulting in poor glycemic control and medication non-adherence (Ali et al., 2010; Liu et al., 2020) and impair of quality of life (Rias, Kurniasari, et al., 2020). However, no epidemiological evidence has spesifically investigated the relationship between anxiety and determinats factor of T2DM in Indonesia with large respondents. Thus, research on the threat of anxiety among individulas with T2DM in Indonesia should be undertaken.

In addition, both male and female with anxiety show significantly unique characteristic of co-occurring psychiatric disorders. Gender differences in anxiety disorders tend to be determined by both sociocultural and biological influences (Boehlen et al., 2020). A community-based design with a random sampling study revealed that females who were females more than 1.6-fold likely to have escalated anxiety symptoms compared with those who were male (Sun et al., 2016). Moreover, a previous study confirmed that females experience significantly more anxiety symptoms among people with T2DM in Southern Iran (Dehesh et al., 2020). Hence, determining the relationship between gender differences and anxiety symptoms in Indonesian with T2DM was important.

Remarkably, the white blood cells count (WBCs) is a non-specific inflammatory marker that is typically included in a complete blood count (CBC) panel and an inexpensive biological marker that can detect inflammatory abnormalities (Lee et al., 2014; Rias, Gordon, et al., 2020). Since WBCs is an independent predictor of T2DM (Rias, Gordon, et al., 2020). Moreover, the high levels of WBCs was associated with escalated levels of anxiety (Shafiee et al., 2017). These findings could be suggested that hyperglycemia observed in anxiety patients may be explained by higher WBCs. Consequently, We hypothesize that high level of WBCs may be associated with anxiety among individuals with T2DM, which consequently increase susceptibility to T2DM complication. However, these relationships require clarification.

Indonesian civilians are particularly susceptible to T2DM because of physiological and societal factors (Rias, Gordon, et al., 2020). However, no study has been conducted in a community large sample with stratified multistage cluster sampling in Indonesia on the prevalence of, and factors related to, anxiety symptoms in patients with T2DM. Our study aimed to explore the prevalence of, and the factors related to, anxiety symptoms among individuals with T2DM in Indonesian

RESEARCH METHOD

Participant characteristics and research design

This research design used the cross-sectional study. The inclusion criteria for T2DM were (1) Indonesian nationals with older than 17 until 79 years; (2) those who agreed to participate and completed all assessment; and (3) those who had diagnoses of T2DM validated by the medical doctors by ADA criteria (American Diabetes, 2018). Participants who (1) had ≤24 of mini-mental state exam scores; (2) were pregnant; (3) had a disability; (4) used antidepressants; and (5) had auditory deficiencies were excluded from the study.

Sampling procedures

Between July 01 until November 30, 2018, in the Indonesian province of East Java. Procedures we performed this community-based with stratified multistage cluster sampling. Notably, we fragmented the provincial capital into 38 regions in the first stage. For the second stage, we selected four regions from the 38 available, including two urban and two rural areas. At the final stage, we also randomly selected eight community clinics from the four regions for data collection, three of which rejected our invitation to participate. Overall, five community-based clinics area participated in our work for respondent's recruitment. The institutional review board (IRB) of Siti Khodijah Muhammadiyah Sepanjang Hospital Ethics Committee approved the study protocol (IRB: 009/KET-TPEP/X-2018),

and the protocol was conformed to the provisions of the Declaration of Helsinki. We acquired written informed consent from each respondent after convincing them verbally and written information about this study.

Sample size, power, and precision

This research used sample size software the G-Power version 3.1 with Cohen's effect size of 0.57 (Sun et al., 2016) for the outcome of an expected reduction in the percentage of participants had high level of anxiety diagnosed with T2DM, an alpha level of 0.05, and power value of 0.9. The sample size will be predicted for 262 individuals. Considering an estimated margin error of 12%, thus total sample size was increased to 294 eligible respondents.

Measures and covariates

During the research, all respondents were interviewed by qualified nurses using a standard questionnaire that conceived questions about participants' demographic, such as age, body mass index, sex. Additionally, duration of diabetes, smoking status including smoking and non-smoking, WBCs and anxiety were assessed. The validity and reliability of the questionnaire have been suggested in previous studies (Arifin et al., 2019; Rias, 2017).

The physiological disturbing using the Stress, Anxiety and Depression Questioners (DASS-21) is consists of 21 items (Lovibond & Lovibond, 1995). Moreover, the Cronbach alpha value of the Bahasa translations version is 0.85 for anxiety domains (Oei et al., 2013). This research described DASS-21 as follows: DASS-21 scores for anxiety (yes = score ≥ 8, no = score < 8), was categorized into two groups. All items have 4 response choices (0; did not apply to me at all, 1; applied to me to some degree, or some of time, 2; applied to me to a considerable or good part of time, 3; applied to me to z very much or most of times). The total score can be calculated by summing the overall score obtained from each of the questions. The minimum score is 0 and the maximum score is 63.

The clinical and biochemical measures involved BMI, and WBCs. Research assistants assessed body measurements, including height and weight, as well as checked using medical records. Height and weight were examined by research assistants and make convinced using the medical report. Body mass index was measured as body weight (kg)/height^2(m^2), and we categorized into two category: obese (body mass index ≥ 25) and non-obese (body mass index < 25 kg/m^2) categories (Purnell, 2018). After 12 hours of fasting, all respondents were invited to attend each clinical examination. WBC was calculated using an automated hematology analyzer XP-100. Moreover, WBCs was classified into two categories utilizing receiver operating principle to determine odds ratios (Liu et al., 2017). We defined WBCs as either <7.950 or ≥7.950 (10^3/ml) based on the area under the curve (AUC) of .660, with 61% specificity and 63% sensitivity.

Data analysis

Allocations of demographic information and predictors variables between group among T2DM patients were explored using frequency (number) and percentage (percent) and studied using either Chi-Square statistics or Fisher-test. Association between variables was evaluated using Pearson's test, Spearman's test or ANOVA, where applicable. More, a simple logistic regression was accessed to quantify the unadjusted odds ratio (OR) and assess the bivariate analysis association between gender differences, WBCs and anxiety. Following the multiple logistic regression for T2DM in relation to exposures of interest an adjusted odds ratio (AOR) and the corresponding 95% confidence interval (CIs) were obtained after adjustment for possible confounding variables in models (age, marital status, economic status, education, smoking habits, and BMI).

RESULTS AND DISCUSSION

To the best of our knowledge, the present study is the first to explore the association of WBCs with Anxiety among individuals with T2DM in an Indonesian civilian. Our results demonstrated that both WBCs ≥7.576 and female were associated with higher level of anxiety among patients with T2DM in Indonesia.

Table 1 shows that, the demographic characteristics of the participants. There were no significant differences by age, marital status, economic and education between individulas with anxiety and non-anxiety among individuals with T2DM. However, we did find a significant difference by gender was revealed between the groups.

Table 1
Distributions of Demographic Characteristics between Non-Anxiety and Patients with Anxiety among T2DM (N = 294).

Characteristic	Total Participants (n = 294) n (%)	Non-Anxiety (n = 62) n (%)	Anxiety (n = 232) n (%)	p value
Age[b]	54.44 ± 6.92	56.19 ± 6.77	55.24 ± 6.96	0.334
Sex[a]				
Male	57 (19.4)	5 (20.1)	52 (22.4)	0.011*
Female	237 (80.6)	57 (79.9)	180 (77.6)	
Marital status[a]				
Not married	159 (54.1)	34 (54.8)	125 (53.9)	0.893
Married	135 (45.9)	28 (45.2)	107 (46.1)	
Economic status (IDR)[a]				
Hight income	39 (13.3)	11 (17.7)	28 (12.1)	0.242
Low income	255 (86.7)	51 (82.3)	204 (87.9)	
Education[a]				
ISCED <3	169 (57.5)	38 (61.3)	131 (56.5)	0.495
ISCED ≥3	125 (42.5)	24 (38.7)	101 (43.5)	

Notes. T2DM: type 2 diabetes mellitus; SD: standard deviation; IDR: Indonesian Rupiah rate; ISCED: International

Standard Classification of Education. Data were presented as mean ± SD, frequency and percentage, and *p*-values were calculated using [a]Chi-square test, or Fisher's exact test, where appropriate, and [b]independent sample *t*-test. *A *p* value of <0.05 indicates statistical significance.

We have summarized the determinantal factors for anxiety symptoms in Table 2. We observed significant differences by duration of diabetes and WBCs between individulas with anxiety and non-anxiety among individuals with T2DM. Unfortunately, we did not find a significant difference by smoking status and BMI were shown between the groups.

Table 2. Relationships Distributions of Determinantal Factors between Non-Anxiety and Patients with Anxiety among T2DM (N = 294).

Characteristics	Total Participants (*n* = 294) *n* (%)	Non-Anxiety (*n* = 62) *n* (%)	Anxiety (*n* = 232) *n* (%)	*p* value
Duration of diabetes (years) mean ± SD[b]	4.14 ± 1.58	3.76 ± 1.69	4.24 ± 1.54	0.033*
Smoking status[a]				0.180
Non-smoking	261 (88.8)	58 (93.5)	203 (87.5)	
Smoking	33 (11.2)	4 (6.5)	29 (12.5)	
BMI (kg/m^2)[a]				
<25	178 (60.5)	40 (64.5)	138 (60.5)	0.471
≥25	116 (39.5)	22 (35.5)	94 (40.5)	
WBCs (10^3/μL)[a]				
<7.576	137 (46.6)	39 (62.9)	98 (42.2)	0.004
≥7.576	157 (53.4)	23 (37.1)	134 (57.8)	

Notes. T2DM: type 2 diabetes mellitus; SD: standard deviation; BMI: body mass index; WBCs: white blood cells.

Data were presented as mean ± SD, frequency and percentage, and *p*-values were calculated using [a]Chi-square test, or Fisher's exact test, where appropriate, and [b]independent sample *t*-test. *A *p* value of <0.05 indicates statistical significance.

Values of the AOR and 95% CIs of duration of diabetes, gender, and WBCs, and risk of anxiety symptoms are presented in Table 3. Famale had a 0.26-fold higher risk (95% CI = 0.07– 0.94; *p* = 0.040) of having anxiety compared with male after adjustment for confounding factors. In addition, individulas with a WBCs of ≥7.576 103/μL had a 2.04-fold higher risk (95% CI = 1.12–3.71; *p* = 0.021) of having anxiety symptoms compared with those with a WBCs of <7.576 103/μL after adjustment for confounding variables. Interstingly, no significant association was observed between being duration of diabetes and anxiety after confounding factors were controlled for confounding factors.

Table 3. Adjusted odds ratios and 95% confidence intervals for duratiom of diabetes, gender, WBCs, and Anxiety symptoms risk among T2DM (*N* = 294).

Variables	Unadjusted OR (95% CI)	AOR (95% CI)
Duration of diabetes (years)	1.23 (1.02–1.49) *	1.11 (0.90–1.37)
Gender		
Male	1.00	1.00
Female	0.30 (0.12–0.80) **	0.26 (0.07–0.94) *
WBCs (10^3/μL)		
<7.576	1.00	1.00
≥7.576	2.32 (1.30–4.13) **	2.04 (1.12–3.71) *

Notes. T2DM: type 2 diabetes mellitus; WBCs: white blood cells; OR: odds ratio; CI: confidence interval; AOR: adjusted odds ratio. AOR, adjusted for age, marital status, economic status, education, smoking habits, and BMI. * *p* value of < 0.05, ** *p* value of < 0.01, *** *p* value of < 0.001.

We found that the prevalence rate of anxiety symptoms in patients with T2DM was 78.9%, these finding are in line with reports from other country more than 50% had anxiety such as Iran (Palizgir et al., 2013), Pakistan (Khuwaja et al., 2010), Mexico (Tovilla-Zarate et al., 2012). Additionally, it is stated that psychological disorders such as anxiety are more common in developing countries (Khuwaja et al., 2010). There are many potential reasons for the higher levels of anxiety in developing countries than in developed countries, including increased gender inequality, widespread poverty, lower levels of education, greater levels of poverty, financial struggles, and other socioeconomic stressors (Jiang et al., 2014; Khuwaja & Kadir, 2010), or differences in screening of sampling methods (Sun et al., 2016). Hence, in the T2DM population, anxiety is a problems condition that is usually less obvious but needs alternatives care treatment (Tovilla-

Zarate et al., 2012). Interestingly, our work revealed that an increased duration of diabetes was associated with an increased odds of having anxiety. However, not significantly after adjusted with other covariate variables. Similar fndings have been reported by several studies (Alzahrani et al., 2019; Khuwaja et al., 2010). In contrast, our findings is inconsisten with that of research to significantly and potential factors such as duaration of disease affecting to escalated anxiety symptoms among individuals with T2DM in China. This condition may be related to cumulative vulnerability regarding the time to develop diabetes-related complications is proposed as a possible mechanism underlying the association between the duration of diabetes and anxiety and depression (Alzahrani et al., 2019).

Remarkably, it is well known that being female is significantly correlated within general populations (Biswas

et al., 2020) and also among individulas with T2DM (Dehesh et al., 2020; Sun et al., 2016). Different gender development may be caused by various reasons, including variations in behaviour. Female has been called on to perform a wide range of roles, which requires that they handle greater amounts of work and responsibility. Extroversion and passivity are characteristics that extolled in female (thus giving them social value, thus empowering them to be open and extroverted). In contrast, females' expected social position tends to constrains them, which means that anxiety is twice as prevalent in females than men (Khuwaja et al., 2010; Sun et al., 2016). As has previously been shown, anxiety disorders are more common in the gender that uses people with diabetes. It appears that having diabetes worsens gender disparities in the gender with a higher incidence of these issues rather than conditions, which means that you have to have more of an existing disadvantage to display an anxiety disorder. Another potential explanation for the disparity may be that the test results for men and female prevalence may have been inconsistent is that the data prevalence of men in the study are small (19.4%).

Another key finding in the present study was that higher WBCs was positively relationship with higher levels of anxiety among indivuals with T2DM. In previous study, authors revealed that higher level WBCs were correlated with escalated symptom severity in men (Shafiee et al., 2017) and female (Pitsavos et al., 2006) with anxiety. Moreover, a population-based study with 7516 participants in Iran performed that the WBCs also significantly escalated with the severity anxiety symptoms (Shafiee et al., 2018). Moreover, the leukocyte telomere length was correlated with anxiety(Wang et al., 2017). Notably, the WBCs is an independent predictor of T2DM (Rias, Gordon, et al., 2020), and T2DM is a chronic low-grade inflammatory state characterized by systematic activation of the innate immune system (Zhang et al., 2017). The immune system impairment is a critical factor in the pathogenesis of T2DM. WBCs, as a marker of subclinical inflammation, is inversely related to insulin secretion and is directly related to insulin resistance (Zhang et al., 2017). In various investigations, it has been suggested that sympathetic nervous system activation and the hypothalamic– pituitary adrenal axis both increase the risk of developing atherosclerosis and accelerate the progress of it through behavioral mechanisms (Pitsavos et al., 2006). This mechanism might provide new insight into the pathways that affect anxiety symptoms in patients with T2DM, which could be provided that hyperglycemia observed in anxiety patients may be explained by higher WBCs.

LIMITATION OF THE STUDY

Among the findings of this research is that we collected self-reported anxiety data through the questionnaire, which may result in an underestimate of anxiety's impact and need clarify by physican. Furthermore, even after adjusting for a large number of possible confounding variables, we cannot rule out the possibility that WBCs in individuals with T2DM are influenced by factors other than anxiety. WBCs are reliable, easily quantifiable, and reproducible, but they are nonspecific for anxiety associated with T2DM. Importantly, our finding that decline the WBC levels have a beneficial impact on decline anxiety in patients with T2DM is potentially significant because it could lead to the detection and promotion of low WBCs-targeted strategies for reducing anxiety in patients with T2DM. Additionally, we only focused on WBCs. A future research should look at biomarkers for additional mechanisms, such as oxidative stress or other inflammation biomarkers, in participants with T2DM who experience anxiety or other physiological problems. Finally, a longitudinal study would provide more detailed information about an individual and combined effects of WBCs and other inflammatory biomarkers and pathways on anxiety in patients with T2DM, thus encouraging future nursing research and practice.

CONCLUSIONS AND SUGGESTIONS

Female exhibited significantly higher levels of anxiety than male respondents. Notably, respondents with WBCs of ≥7.576 had significantly higher anxiety than patients with WBCs of <7.576. There was high prevalence of axienty symptoms in this Indonesian sample of respondents. Female and high level of WBCs exist on increasing susceptibility to anxiety symptoms among individuals with T2DM. These findings suggest prominent roles for nurse educators as well as the health professionals in identifying and promoting treatment-targeted strategies such as maintaining a low WBCs and more deep investigation expecialy in female to declined anxiety levels among patients with T2DM.

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Conflict of Interest Statement

The author(s) have disclosed that they have no possible conflicts of interest related to the study, authorship, or publication of this paper.

REFERENCES

Ali, S., Stone, M., Skinner, T. C., Robertson, N., Davies, M., & Khunti, K. (2010). The association between depression and health-related quality of life in people with type 2 diabetes: a systematic literature review. *Diabetes/metabolism research and reviews*, *26*(2), 75-89. https://doi.org/10.1002/dmrr.1065.

Alzahrani, A., Alghamdi, A., Alqarni, T., Alshareef, R., & Alzahrani, A. (2019). Prevalence and predictors of depression, anxiety, and stress symptoms among patients with type II diabetes attending primary healthcare centers in the western region of Saudi Arabia: a cross-sectional study. *International journal of mental health systems*, *13*(1), 1-7. https://doi.org/10.1186/s13033-019-0307-6.

American Diabetes, A. (2018). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care*, *41*(Suppl 1), S13-S27. https://doi.org/10.2337/dc18-S002

Arifin, B., Idrus, L. R., van Asselt, A. D. I., Purba, F. D., Perwitasari, D. A., Thobari, J. A., Cao, Q., Krabbe, P. F. M., & Postma, M. J. (2019). Health-related quality of life in Indonesian type 2 diabetes mellitus outpatients measured with the Bahasa version of EQ-5D [journal article]. *Quality of Life Research*.

https://doi.org/10.1007/s11136-019-02105-z.

Biswas, T., Scott, J. G., Munir, K., Renzaho, A. M., Rawal, L. B., Baxter, J., & Mamun, A. A. (2020). Global variation in the prevalence of suicidal ideation, anxiety and their correlates among adolescents: A population based study of 82 countries. *EClinicalMedicine*, *24*, 100395. https://doi.org/10.1016/j.eclinm.2020.100395.

Boehlen, F. H., Herzog, W., Schellberg, D., Maatouk, I., Schoettker, B., Brenner, H., & Wild, B. (2020). Gender-specific predictors of generalized anxiety disorder symptoms in older adults: Results of a large population-based study. *Journal of affective disorders*, *262*, 174-181. https://doi.org/10.1016/j.jad.2019.10.025.

Bouwman, V., Adriaanse, M. C., Van't Riet, E., Snoek, F. J., Dekker, J. M., & Nijpels, G. (2010). Depression, anxiety and glucose metabolism in the general Dutch population: the new Hoorn study. *PloS one*, *5*(4), e9971. https://doi.org/10.1371/journal.pone.0009971.

Dehesh, T., Dehesh, P., & Shojaei, S. (2020). Prevalence and Associated Factors of Anxiety and Depression Among Patients with Type 2 Diabetes in Kerman, Southern Iran. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *13*, 1509. https://doi.org/10.2147/DMSO.S249385.

Fazelian, S., Amani, R., Paknahad, Z., Kheiri, S., & Khajehali, L. (2019). Effect of vitamin D supplement on mood status and inflammation in vitamin D deficient type 2 diabetic women with anxiety: a randomized clinical trial. *International journal of preventive medicine*, *10*. https://doi.org/10.4103/ijpvm.IJPVM_174_18.

Jiang, Y., Dong, W., Mao, F., Zhang, C., Ding, X., Pan, X., Zhang, Y., Huang, Y., & Dong, J. (2014). Evaluation on the status quo of self monitoring of blood glucose and self-efficacy of diabetes patients in community. *Zhonghua yu Fang yi xue za zhi [Chinese Journal of Preventive Medicine]*, *48*(8), 710-714.

Khuwaja, A. K., & Kadir, M. M. (2010). Gender differences and clustering pattern of behavioural risk factors for chronic non-communicable diseases: community-based study from a developing country. *Chronic illness*, *6*(3), 163-170. https://doi.org/10.1177/1742395309352255.

Khuwaja, A. K., Lalani, S., Dhanani, R., Azam, I. S., Rafique, G., & White, F. (2010). Anxiety and depression among outpatients with type 2 diabetes: A multi-centre study of prevalence and associated factors. *Diabetology & metabolic syndrome*, *2*(1), 1-7. https://doi.org/10.1186/1758-5996-2-72

Lee, C.-T. C., Harris, S. B., Retnakaran, R., Gerstein, H. C., Perkins, B. A., Zinman, B., & Hanley, A. J. (2014). White blood cell subtypes, insulin resistance and β-cell dysfunction in high-risk individuals - the PROMISE cohort. *Clinical Endocrinology*, *81*(4), 536-541. https://doi.org/10.1111/cen.12390.

Liu, S., Zheng, H., Zhu, X., Mao, F., Zhang, S., Shi, H., Li, Y., & Lu, B. (2017). Neutrophil-to-lymphocyte ratio is associated with diabetic peripheral neuropathy in type 2 diabetes patients. *Diabetes research and clinical practice*, *130*, 90-97. https://doi.org/10.1016/j.diabres.2017.05.008.

Liu, X., Haagsma, J., Sijbrands, E., Buijks, H., Boogaard, L., Mackenbach, J. P., Erasmus, V., & Polinder, S. (2020). Anxiety and depression in diabetes care: longitudinal associations with health-related quality of life. *Scientific Reports*, *10*(1), 1-9. https://doi.org/10.1038/s41598-020-57647-x.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour research and therapy*, *33*(3),

335-343. https://doi.org/10.1016/0005-7967(94)00075-U

Oei, T. P. S., Sawang, S., Goh, Y. W., & Mukhtar, F. (2013). Using the Depression Anxiety Stress Scale 21 (DASS-21) across cultures. *International Journal of Psychology*, *48*(6), 1018-1029. https://doi.org/10.1080/00207594.2012.755535.

Ogurtsova, K., da Rocha Fernandes, J. D., Huang, Y., Linnenkamp, U., Guariguata, L., Cho, N. H., Cavan, D., Shaw, J. E., & Makaroff, L. E. (2017). IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract*, *128*, 40-50. https://doi.org/10.1016/j.diabres.2017.03.024.

Palizgir, M., Bakhtiari, M., & Esteghamati, A. (2013). Association of depression and anxiety with diabetes mellitus type 2 concerning some sociological factors. *Iranian Red Crescent Medical Journal*, *15*(8), 644. https://doi.org/10.5812/ircmj.12107.

Pitsavos, C., Panagiotakos, D. B., Papageorgiou, C., Tsetsekou, E., Soldatos, C., & Stefanadis, C. (2006). Anxiety in relation to inflammation and coagulation markers, among healthy adults: the ATTICA study. *Atherosclerosis*, *185*(2), 320-326. https://doi.org/10.1016/j.atherosclerosis.2005.06.001.

Purnell, J. Q. (2018). Definitions, classification, and epidemiology of obesity. *Endotext [Internet]*.

Rias, Y. A. (2017). Hubungan pengetahuan dan keyakinan dengan efikasi diri penyandang diabetic foot ulcer. *Jurnal Keperawatan Muhammadiyah*, *1*(1). Retrieve from: http://103.114.35.30/index.php/JKM/article/view/RA.

Rias, Y. A., Gordon, C. J., Niu, S. F., Wiratama, B. S., Chang, C. W., & Tsai, H. T. (2020). Secondhand Smoke Correlates with Elevated Neutrophil-Lymphocyte Ratio and Has a Synergistic Effect with Physical Inactivity on Increasing Susceptibility to Type 2 Diabetes Mellitus: A Community-Based Case Control Study. *International journal of environmental research and public health*, *17*(16), 5696 https://doi.org/10.3390/ijerph17165696

Rias, Y. A., Kurniasari, M. D., Traynor, V., Niu, S. F., Wiratama, B. S., Chang, C. W., & Tsai, H. T. (2020). Synergistic effect of low neutrophil–lymphocyte ratio with physical activity on quality of life in type 2 diabetes mellitus: A community-based study. *Biological research for nursing*, *22*(3), 378-387.

Rias, Y. A., Kurniawan, A. L., Chang, C. W., Gordon, C. J., & Tsai, H. T. (2020). Synergistic effects of regular walking and alkaline electrolyzed water on decreasing inflammation and oxidative stress, and increasing quality of life in individuals with type 2 diabetes: A community based randomized controlled trial. *Antioxidants*, *9*(10), 946. https://doi.org/10.1177/1099800420924126.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A. A., & Ogurtsova, K. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, *157*, 107843. https://doi.org/10.1016/j.diabres.2019.107843.

Shafiee, M., Ahmadnezhad, M., Tayefi, M., Arekhi, S., Vatanparast, H., Esmaeili, H., Moohebati, M., Ferns, G. A., Mokhber, N., & Arefhosseini, S. R. (2018). Depression and anxiety symptoms are associated with prooxidant-antioxidant balance: A population-based study. *Journal of affective disorders*, *238*, 491-498. https://doi.org/10.1016/j.jad.2018.05.079.

Shafiee, M., Tayefi, M., Hassanian, S. M., Ghaneifar, Z., Parizadeh, M. R., Avan, A., Rahmani, F., Khorasanchi, Z., Azarpajouh, M. R., & Safarian, H. (2017). Depression and anxiety symptoms are associated with white blood cell count and red cell

distribution width: a sex-stratified analysis in a population-based study. *Psychoneuroendocrinology*, *84*, 101-108. https://doi.org/10.1016/j.psyneuen.2017.06.021.

Sun, N., Lou, P., Shang, Y., Zhang, P., Wang, J., Chang, G., & Shi, C. (2016). Prevalence and determinants of depressive and anxiety symptoms in adults with type 2 diabetes in China: a cross-sectional study. *BMJ open*, *6*(8). https://doi.org/10.1136/bmjopen-2016-012540.

Tovilla-Zarate, C., Juarez-Rojop, I., Jimenez, Y. P., Jiménez, M. A., Vázquez, S., Bermúdez-Ocaña, D., Ramón-Frías, T., Mendoza, A. D. G., García, S. P., & Narváez, L. L. (2012). Prevalence of anxiety and depression among outpatients with type 2 diabetes in the Mexican population. *PLoS one*, *7*(5), e36887. https://doi.org/10.1371/journal.pone.0036887.

Wang, X., Sundquist, K., Hedelius, A., Palmér, K., Memon, A. A., & Sundquist, J. (2017). Leukocyte telomere length and depression, anxiety and stress and adjustment disorders in primary health care patients. *BMC psychiatry*, *17*(1), 1-10. https://doi.org/10.1186/s12888-017-1308-0.

Zhang, H., Yang, Z., Zhang, W., Niu, Y., Li, X., Qin, L., & Su, Q. (2017). White blood cell subtypes and risk of type 2 diabetes. *Journal of Diabetes and its Complications*, *31*(1), 31-37. https://doi.org/10.1016/j.jdiacomp.2016.10.029