Factors Influence GLUT-4 Levels of Type 2 Diabetes Mellitus Patients in Medan City, Indonesia

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Abstract. The resistance of insulin in type 2 Diabetes mellitus patients (T2DM) will have a significant impact on glucose regulation with Glucose transporter-4 (GLUT-4) translocation. Glucose transporter-4 plays an essential role in the transport of glucose to most cells. The study design was analytic with a cross sectional approach. The study population was T2DM patient in Medan City with the number of people who have fulfilled the inclusion and exclusion criteria amount 83 patients. Data collection is done by interviewing and patient blood test. Assessment of physical activity of diabetic patients using a global questionnaire physical activity (GPAQ). GLUT-4 levels were assessed using Human Glut-4 with ELISA Method. The nutritional status and history of drug use by direct measurement and interviews. Data analysis using independent T-test with SPSS computer program. The results showed there was a relationship between physical activity and obesity with levels of GLUT-4 ($p < 0.05$), and there was no relationship between consumption of drugs with levels of GLUT4 ($p < 0.05$). By increasing physical activity, proper nutrition management and weight control will help improve insulin sensitivity so that it can control blood sugar levels in T2DM patients

Keywords: GLUT4, physical activity, obesity, blood glucose level.

1 Introduction

Diabetes mellitus refers to a group of common metabolic disorders that share a hyperglycemic phenotype, which is characterized by an increase in circulating glucose concentrations associated with abnormalities in fat, carbohydrate and protein metabolism. Type 2 diabetes is a complex disorder due to peripheral insulin resistance, combined with relative insulin deficiency (Alam et al., 2016). Resistance or insulin deficiency will have a significant impact on glucose regulation with GLUT-4 translocation. Insulin works through a second intermediate system to cause increased transport of glucose outside the cell membrane. Glucose transporter molecules called GLUT-4 glucose transporters to play an essential role in the transport of glucose to most cells. Glucose can be used immediately to produce energy through the Krebs cycle or can store in cells as glycogen. Glucose that enters the cell causes blood glucose levels to decrease, thereby reducing the stimulation of further insulin release (Sayem et al., 2018). Glucose Transporter Type-4 (GLUT-4) is insulin-sensitive GLUT and is expressed on the plasma membrane and organelles of skeletal muscle, heart muscle and adipose tissue for glucose upregulated by insulin (Murray et al, 2014)

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GLUT-4 reacts to an increase in plasma insulin levels rapidly by producing an increase in glucose transport 20-30 times. Without insulin or exercise stimulation, 90% GLUT-4 is sequestering in skeletal and adipose muscle tissue cells in the form of double-layered lipid membranous vesicles. On the cell surface, GLUT-4 facilitates passive diffusion of circulating glucose if glucose concentration in skeletal and adipose muscle tissue decreases (Alam et al., 2016). Several things can influence GLUT-4 levels in the body. Its formation can increase and decrease depending on what influences it. Diet, exercise and medication interventions can increase the formation of GLUT-4 while obesity, chronic disease, and some inflammatory mediators can inhibit its formation. Therefore, GLUT-4 can use as a potential therapeutic target in the management of type 2 DM. (Alam et al., 2016). This study aimed to analyse factors that Influence GLUT-4 Levels ofType 2 Diabetes Mellitus Patients in Medan City, Indonesia.

2 Material And Method

The study design was analytic with a cross sectional approach. The collection of data has conducted in April-May 2018. The population study was Type 2 Diabetes Mellitus patient (T2DM) in Medan City that collected from several community health centres and general practice doctors serving outpatient diabetes patients in Medan City. The sample size is about 83 patients with the inclusion criteria were: Patients with type 2 diabetes aged 35-55 years, had no contraindication to doing physical exercise, willing to follow the research and the patient Came Independently to the place of service and independent in performing daily activities. While Exclusion Criteria are: Patients with severe complications, type 1 diabetes mellitus patients, another type, and gestational, type 2 diabetes mellitus patients accompanied by other comorbidities.

The research ethics committee has approved the research protocol at the Faculty of Medicine, Universitas Sumatera Utara and all participants who are willing to participate in the research have signed written informed consent. Research data sources are primary data. Body Mass Index patients do to the determination of nutritional status, the determination of treatment done by treatment history anamneses (crosscheck with the patient's status), physical activity assessment done by using the instrument Global Physical Activity Questionnaire (GPAQ). The Global Physical Activity Questionnaire assessed the activities carried out by diabetic patients (in the last seven days) and stated with MET (Metabolic Equivalent). For examination of GLUT4 using inspection with ELISA technique with Human Instrument GLUT4 (Glucose Transporter 4) ELISA Kit instrument Human GLUT4 (Glucose Transporter 4) ELISA Kit. The kit was based on sandwich enzyme-linked immune-sorbent assay technology. Anti- GLUT4 antibody was pre-coated onto 96-well plates. And the biotin-conjugated anti- GLUT4 antibody was used as detection antibodies.Data analysis using Independent T-Test using SPSS computer program.

3 Result And Discussion

3.1 Baseline Characteristics of T2DM patients In Medan City

Table 1. Basic Characteristics of Diabetes Melitus Type 2 patients in Medan City.

Characteristics	Frequency (n)	Characteristics (%)
Gender		
Man	16	19.3
Woman	67	80.7
Age Group		
36-45 years old	12	14.5
46-55 years old	71	83.5
Duration of Illness		
1-5 years	50	60.2
6-10 years	20	24.1
11-15 years	11	13.3
> 15 years	2	2.4
Diabetes History		
Father	15	18.1
Mother	15	18.1
Father and Mother	8	9.6
None	45	54.2
Use of Anti-Diabetic Drugs		
Glibenclamide	66	79.5
Metformin	17	20.5
BMI		
Obesity	49	59.0
Non Obesity	34	41.0
Blood Pressure (Systole)		
Hypertension	66	79.5
Not Hypertension	17	20.5
Physical Activity (PA)		
Good PA	32	38.6
Less PA	51	61.4

Table 1 shows that many diabetic patients in this study were 67 women (80.7%), most elderly patients about 71 elderly (83.5%), the duration of diabetes known to most of the diabetes for 1-5 years as many as 50 people (60.2%), the family history known have a family history of diabetes suffered by the mother as much as 45 people (54.2%). The majority of diabetic patients consume glibenclamide as an anti-diabetic drug as much as 66 people (79.5%). Nutritional status of diabetes patients most with obese as many as 41 people (49.4%), about 66 people (79.5%) with hypertension and majority has less physical activity 51 people

(61.4%).mellitus patients, another type, and gestational, type 2 diabetes mellitus patients accompanied by other comorbidities.

3.2 Relation of Physical Activity, Obesity and Consumption of Drugs with GLUT4 in Type 2 Diabetes Mellitus Patients in Medan City

Table 2. Relation of Physical Activity, Obesity and Consumption of Drugs with GLUT4 in Type 2 Diabetes Mellitus Patients in Medan City.

Parameter	GLUT4 (ng/ml)	P
Physical Activity		
Good	2.7	0.04
Less	2.2	
Medical Treatment		
Metformin	2.3	0.44
Non Metformin (Glibencklamid)	2.4	
BMI		
Obese	2.2	0.03
Non Obese	2.6	

shows that patients who have good physical activity have an average GLUT4 level higher than those who do not have good physical activity. Patients who received Metformin and not Metformin (Glibenclamide) therapy there was no average difference significant between the two in a sound manner, for the nutritional status it is known that there are differences in the average levels of GLUT4 based on obese and non-obese patients. In conclusion, there is a difference in average GLUT4 based on physical activity and nutritional status (p,0.05), while there is no difference in drug use (p>0.05).

The results of the study stated that there was a relationship between physical activity and levels of GLUT4, the more physical activity carried out would increase the secretion of GLUT4. This study is in line with the research conducted by Guelfi (2012) that there is a positive correlation between the total work done and the number of GLUT-4 translocations in recorded subjects. Physical activity or exercise is believed to control blood sugar in T2DM patients. Some things that need to consider in physical activity or exercise are the type and intensity, physical fitness level, nutritional status, meal schedule, medications used and degree of glucose control (Sinaga, 2016; Kennedy, 2012).

Physical exercise coupled with dietary modifications and drugs have recommended for one of the four components for diabetes therapy, in a study found that exercise can reduce hyperglycemia and body fat and improve protection against the development of cardiovascular complications. Regular physical exercise reduces dyslipidemia and increases insulin sensitivity. By increasing the concentration of GLUT-4 receptors on the plasma membrane or sarcoma, insulin resistance affects the transport of glucose into cells. The glycemic control, visceral fat reduction, and decreased plasma triglycerides can be achieved without drastic weight loss (Aggarwala et al., 2016). Physical exercise plays a vital role in the prevention and control of T2DM, insulin resistance, prediabetes, diabetes gestational Mellitus and health complications related to diabetes. Both aerobic exercise and endurance increase insulin work

and also help in the management of blood glucose levels, lipids, and blood pressure. Most people with T2DM can exercise safely as long as certain precautions (Syed Shakil, 2017).

Moderate intensity exercise can increase temporary GLUT-4 gene expression. GLUT-4 protein increase can occur after 1.5 hours to 24 hours after exercise. GLUT-4 protein enhancement and mediated by myocyte enhancer factor-2 (MEF-2) (Kraniou et al., 2006; Richter and Hargreaves, 2013; Handoko and Purwanto, 2017). In people with T2DM, there is a decrease in GLUT-4 levels which can see an increase in postprandial blood glucose. Management of diabetes continues to develop until now, and one of them is with exercise that can potentially increase muscle GLUT-4 levels (Handoko and Purwanto, 2017). During glycogen activity is the most significant source of fuel for muscle movement when glycogen begins to decrease, muscles increase blood glucose intake and use along with the release of free fatty acids from fat tissue. The transport of glucose to muscle tissue is carried out by GLUT-4, insulin activates GLUT-4 translocation to complex cascade signals. Contractions stimulate GLUT-4 translocation by activating 5-AMP-protein kinase. Insulin stimulation of GLUT-4 translocation is disrupted generally in patients with T2DM. Aerobic physical exercise and endurance can increase GLUT-4 and blood glucose retrieval even in the condition of type 2 diabetes mellitus. In T2DM patients who do moderate activity, the use of blood glucose by muscle tissue increases which results in decreased blood glucose levels (Alam et al., 2016).

Research conducted by Richter and Hargreaves (2013) states that muscle contraction can trigger theinsertion of GLUT-4 into the plasma of active muscle cells. During physical exercise, coordinated increase in skeletal muscle blood flow, capillary recruitment, GLUT-4 translocation to sarcolemma and T-tubule, and membranes are all critical for the absorption of glucose and oxidation. GLUT-4 translocation to sarcoma and tubules-T is the basis for the absorption of skeletal muscle glucose and includes the retrieval of GLUT-4 from intracellular storage. For absorption of glucose during exercise depends on exercise conditions which are determined primarily by the intensity and duration of the exercise. Research conducted by Richter and Hargreaves (2013) also mentioned that transient activity could increase GLUT-4 mRNA rapidly while after activity and last up to 24 hours this is related to MEF-2 which activates GLUT-4 promoter and increases GLUT-4 protein, but the effect of GLUT-protein levels increases 4 This is only temporary when compared to regular training.

The results showed that there was no effect of consumption of oral anti-diabetic drugs (Metformin) with levels of GLUT4. One of the antidiabetic drugs that can affect GLUT-4 levels is metformin. This metformin is a biguanide drug that comes from Galegaofficinalis. This drug has many effects on insulin sensitivity in the muscles and in the liver, including stimulating GLUT-4 translocation by increasing Casitas B-lineage Lymphoma (Cbl) phosphorylation inAdenosine Monophosphate Dependent Protein Kinase (AMPK). Adenosine Monophosphate Dependent Protein KinaseActivated Protein Kinase (AMPK) is an enzyme that plays a role in cellular energy homeostasis. AMPK is activated when cellular energy has to reduce. When phosphorylation of Threonine residue (thr), AMPK will increase the catabolic pathway that produces ATP, namely glycolysis and fatty acid oxidation, thereby increasing the translocation of GLUT-4. (Garabadu , 2017; Yagasaki, 2014). Metformin also increases the production and secretion of adiponectin, so that ultimately it will improve insulin resistance and prevent the conversion of prediabetes to diabetes type 2 (Woods 2003; Manaf et al., 2008). With the increased sensitivity of insulin receptors, of course, GLUT4 secretion will also increase. Research conducted by Manaf et al. (2008) found that administration of metformin for 12 weeks increased levels of adiponectin in the obese group with prediabetes and increased levels of adiponectin after metformin administration, moderately correlated with

decreased triglyceride levels, and weakly correlated with increased HDL cholesterol levels and decreased LDL cholesterol levels (Amelia et al., 2017). This study found no relationship, this can be caused by more patients who were given Glibenclamide drugs compared to metformin, then from patients who received OAD there were still many of them who did not regularly take medication there were some patients who had not eaten drugs for a long time. Only consume traditional medicines such as decoction of leaves.

This study showed that there was a relationship between obesity and GLUT4 levels, the increase in body weight would disrupt the sensitivity of insulin receptors, and this would cause a decrease in secretion from GLUT4. Overweight and obesity are an excessive accumulation of adipose tissue that can interfere with both physical health and psychosocial health (Al-Goblan et al., 2014). Obesity and T2DM have a connection with to insulin resistance. Adipose tissue affects metabolism by secreting hormones, glycerol, and other substances such as leptin, cytokines, adiponectin, and proinflammatory substances, and by secreting NEFAs. In obese people, the secretion of all these substances increases. The inflammatory substances produced will participate in causing insulin resistance. The resulting inflammatory substances include IL-1 and TNF-α. (Al-Goblan et al., 2014; Ali, 2014; Van der Heijden et al., 2018; Amelia, 2017)

TNF-α can interfere with GLUT-4 translocation to the plasma membrane by damaging the insulin signaling pathway. The increase in TNF-α will cause cessation of phosphorylation of tyrosine residues in IRS1 but phosphorylation of serine (nonfunctional) residues that inhibit the work of IRS1. That way the translocation process from GLUT-4 will disrupt (Mohd-Radzman et al., 2013; Ali, 2014).

In obese people, there will be a slow but sure resistance to the cellular action of insulin which is manifested by reduced insulin ability to inhibit glucose secretion from the liver and its ability to support glucose uptake in fat and muscle (Park, 2006). Insulin-related insulin resistance is a complex disorder involving various mechanisms. Progress in molecular biology research has made it immense to find many things related to insulin resistance compared to ten years ago. Many mechanism pathways are simultaneously interrupted, and when one pathway is interrupted, the interconnection with another line will result in changes to other systems. The mechanism that occurs is related to many pathways and mediators. The weight control is closely related to blood sugar control and will ultimately prevent complications and improve quality of life (Amelia et al., 2018).

4 Conclusions

Physical activity and nutritional status are factors has strong related to lifestyle and affect GLUT4 secretion, by improving lifestyles T2DM patients can control their blood sugar levels so that they avoid complications and have a good quality of life.

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