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Beta Cell Pancreas Dysfunction and Hyperglycemia in Patient Schizophrenia that Uses Haloperidol at Region Special Dadi Hospital Province South Sulawesi

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Abstract

Schizophrenic patients at high risk for development of type 2 diabetes as a side effect of the antipsychotic medication This research is aimed to find out (1) the level of HbA1c and the description of hyperglycemia incidence, (2) the value of HOMA-β and the description of beta cell dysfunction incidence, (3) the correlation between HOMA-β value with HbA1c level, (4) the duration correlation between the use of haloperidol with the HOMA-β value and the HbA1c level, (5) the duration correlation the use of haloperidol and the HbA1c level through HOMA-β value. This study was conducted at the inpatient ward of Dadi Hospital, South Sulawesi Province using quantitative method with cross sectional study. By using total sampling way, 64 were chosen. The data were then analyzed by using frequency distribution test and Spearman correlation. The result of the study indicates that sufferer schizophrenia at Dadi Hospital who use haloperidol have problems of hyperglycemia (HbA1c >5,5%). The longer the use of haloperidol the more the excelsior level of HbA1c found. About 4,3% hyperglycemia in use of haloperidol <1 year and 23,9% in use >1 year. The mechanism the hyperglycemia incidence mentioned above suffered through dysfunction of beta cell. The longer the use of haloperidol the lower the HOMA-β value. It reaches 28,3% dysfunction of beta cell in use of haloperidol <1 year and 54,3% in use >1 year.

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The dysfunction of beta cell has relation with the duration in the use of haloperidol. The lower HOMA-β value level the more the excelsior level of HbA1c. The incidence of Hyperglycemia is correlated with the dysfunction of beta cell.

Keywords: Antipsychotic; haloperidol; beta cell dysfunction; hyperglycemia; HOMA-β and HbA1c.

1. Introduction

Schizophrenic patients at high risk for development of type 2 diabetes as a side effect of the antipsychotic medication. Prevalence of DM reported two to three-fold higher in patients with schizophrenia who received antipsychotics compared with the general population [1]. In addition, there was no difference between patients receiving typical and atypical antipsychotics, although some opinions supporting that abnormalities in blood sugar may be higher with atypical than typical antipsychotic medications [2,3]. The main pathogenesis of type 2 diabetes, the insulin disorders due to insulin resistance and impaired insulin secretion, due to dysfunction of beta cells (β) of the pancreas, which in turn can lead to hyperglycemia [4]. Research by Lindanmayer [5], said that the antipsychotic haloperidol can increase fasting blood sugar and insulin resistance through hyperprolactinemia, but not on resperidon. Fasting blood glucose levels also directly proportional to the duration of use haloperidol, where the longer used, the higher the blood glucose levels [6]. However, the different results obtained by Hendenmalm [7] which says that haloperidol was not associated with impaired glucose intolerance.

The mechanism of conventional antipsychotics (haloperidol) which causes toxic is not fully understood. However, some experts said through an increase in weight, which is associated with insulin resistance mechanism. The increase in weight due to the use of antipsychotics is mediated by histamine H1 receptor, activating the hypothalamic AMP kinase, which can increase food intake [8].

Proposed different Liorente and Urrutia [9], that the complications of hyperglycemia and diabetes in the administration of antipsychotic, can occur without changes in body weight. Thus, the toxic effects of antipsychotics on pancreatic beta cells, have an important role in the pathogenesis of type 2 diabetes.

An in vitro study suggests that, haloperidol can affect the electrical activity in pancreatic beta cells, which give a toxic effect on the permeability of potassium, although the mechanism is not yet known [10]. In addition, the chronic use of haloperidol was associated with increased incidence of impaired glucose tolerance and type 2 diabetes, by blocking KATP channels through the inhibition of Kir 6.2 / SUR1 the KATP channel. However, the inhibitory effects of haloperidol on KATP not through D2 receptors [11]. Based on the above, the researcher was interested to study pancreatic beta cell dysfunction and hyperglycemia, in patients with schizophrenia who use haloperidol.

2. Materials and Methods

This study uses a quantitative approach to the type of cross sectional study. Data collection techniques in this study is the interview, physical examination, laboratory tests. To see the proportion of beta cell dysfunction and incidence of hyperglycemia, used test frequency distribution, and to see the relationship between the two

variables, Spearman correlation test.

3. Result

Based on this research, the data obtained respondent characteristics as shown in Table 1.

Table 1: Characteristics of respondent data

Variable	N	Mean	Median	SD	Min	Max
Age of respondents	46	33,83	32,5	9,33	17	59
Fasting Plasma Glucose (FPG)	46	4,74	4,69	0,44	3,83	5,89
Fasting Plasma Insulin (FPI)	46	3,76	2,37	3,17	2,00	19,30
Homa β	46	68,86	47,00	62,88	16,70	365,70
Homa β < 1 year	17	70,42	30	87,0	16,70	365,70
Homa β > 1 year	29	67,94	56,6	45,03	21,20	221,40
HbA1c	46	5,26	5,00	0,58	4,00	7,00
HbA1c < 1 year	17	5,06	5,00	0,43	4,00	6,00
HbA1c > 1 year	29	5,38	5,00	0,62	4,00	7,00

Source: Primary Data

3.1 The proportion of beta cell dysfunction and incidence of hyperglycemia by Duration Use of Haloperidol (DUH)

To determine the proportion of beta cell dysfunction and incidence of hyperglycemia in patients with schizophrenia who use haloperidol, used statistical test frequency distribution. From the research, the data obtained as shown in Table 2 and Figure 6, 7 and 8.

3.2 Beta cell dysfunction and hyperglycemia on Usable Haloperidol

To determine the relationship longer use haloperidol beta cell dysfunction and hyperglycemia, using Spearman correlation test, in accordance with Table 3.

Table 2: Differences in the distribution of β cell dysfunction and hyperglycemia by long use of haloperidol

Parameter	Use haloperidol < 1 year (n = 17)	Use haloperidol > 1 year (n = 29)	OR	95% Confidence interval	
	n (%)	n (%)		Lower	Upper
	13 (28,3)	25 (54,3)	1,923	0,413	8,965
Beta cell dysfunction Normal	4 (8,7)	4 (8,7)			
Abnormal HbA1c	2 (4,3)	11 (23,9)	4,583	0,876	23,988
Normal	15 (32,6)	18 (39,1)			
Abnormal FPG	2 (4,3)	1 (2,2)	0,268	0,022	3,202
Normal	15 (32,6)	28 (60,9)			

Source: Primary Data

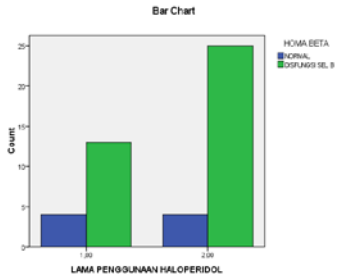

Figure 6: Graph beta cell dysfunction by long use of haloperidol

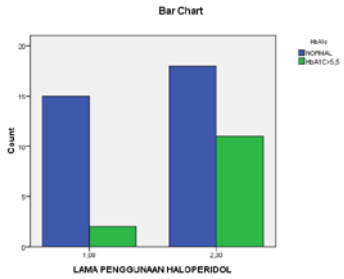

Figure 7: Graph abnormal HbA1c by long use of haloperidol

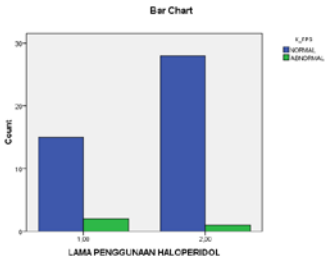

Figure 8: Graph abnormal FPG by long use of haloperidol

4. Discussion

Based on the research results, it was found that the data between the duration of use of haloperidol with beta cell dysfunction there is no meaningful relationship, with ap value of 0.129 and a correlation coefficient of 0.227, which means there is a positive correlation with the strength of a weak correlation, where the longer the respondents using haloperidol, then the possibility of the higher beta cell dysfunction. In addition, the data between the duration of use of haloperidol with hyperglycemia, there is no meaningful relationship, based on HbA1c, with ap value of 0.063 and a correlation coefficient of 0.276, which means there is a positive correlation with the strength of a weak correlation, where the longer the respondents using haloperidol, then the higher the tendency of hyperglycemia. This can be seen in Table 3.

Table 3: Correlation duration of the use haloperidol with HOMA- value β, and HbA1C

Parameter	correlation coefficient (r)	Probability (p)
DUHvs HOMA-β	0,227	0,124
DUHvs HbA1c	0,276	0,063
HOMA-β vs HbA1c	0,288	0,052

Source: Primary Data

Based on the above, it can be concluded that it is in line with the existing theory that the use of antipsychotic haloperidol may cause hyperglycemia through toxic effects on beta cells. The results showed that, using haloperidol schizophrenic prone to hyperglycemia. Researchers assume, possibly through beta cell dysfunction, therefore the study found a decrease in the value of HOMA-β. Hyperglycemia not through insulin resistance, therefore none of patients who are obese, according to their Body Mass Index (BMI).

Haloperidol can affect the electrical activity in pancreatic beta cells, which give a toxic effect on the permeability of potassium, although the mechanism is unknown [10]. This is consistent with the theory that, increased permeability of the ATP-sensitive K channels will cause potassium ions leave the beta cells (K-efflux), thereby maintaining the membrane potential in a state of hyperpolarization, which causes depolarization hard going, so that Ca-channels remain closed, consequently calcium cannot get into the beta cells, so that stimulation of beta cells to secrete insulin exocytosis decreased. This condition will cause the cell glucose uptake decreased, which results in an increase in blood glucose levels [12].

Moreover, the tendency of beta cell dysfunction and hyperglycemia in this study, supported by studies conducted [11], that the chronic use of haloperidol were associated with an increased incidence of impaired glucose tolerance and type 2 diabetes, by blocking KATP channels through the inhibition of the Kir 6.2 / SUR1 the KATP channel. However, the inhibitory effects of haloperidol on KATP not through D2 receptors. In contrast presented by Rubi Blanca [13],that the antipsychotic drugs block dopamine receptors can cause hyperinsulinemia, hypoglycemia, increased appetite and obesity are associated with DM. Normally, dopamine transporter Glut assist in cell glucose uptake. Consequently, inhibition D2R will lead to hyperglycemia, resulting in hyperinsulinemia. In addition, there is the theory that dopamine D2 receptors inhibit haloperidol. Where is the dopamine D2 receptor in beta cells play a role in the regulation of blood glucose levels, with inhibition of insulin secretion [14].

Increased secretion of dopamine can reduce ACH [15]. Thus, inhibition of dopamine D2 receptors may increase the ACH (adrenocorticotropin hormone), which triggers increased cortisol, so gluconeogenesis increased to ten-fold, resulting in an increase in blood glucose levels [16].

Other mechanisms that explain the relationship of the use of antipsychotics with type 2 diabetes is through the effect on cholinergic, which can stimulate insulin secretion and activates phospholipase C, which is mediated by

the muscarinic M3 receptor in beta cells [17].

Based on theory and research data, researchers can conclude that the use of haloperidol may cause hyperglycemia through beta cell dysfunction, based on the cut-off point of the research Ciampelli [18] (HOMA β <107), where it can cause a decrease in insulin secretion. As a result, the cells decreased glucose uptake, resulting in hyperglycemia. No meaningful relationship between the duration of use of haloperidol with hyperglycemia and beta-cell dysfunction, caused by the limited number of samples, based on the attached sample rechecking. However, the research can provide meaning that there is a tendency to hyperglycemia and beta cell dysfunction, which in the study were measured by HOMA β and HbA1c examination, where the longer use of haloperidol, the incidence of beta cell dysfunction and hyperglycemia higher, which will eventually lead to type 2 diabetes.

This is in line with the source stating that the prevalence of diabetes mellitus in patients with schizophrenia who received antipsychotic two to three times higher than the general public or which do not suffer from schizophrenia [19]. In addition, there was no difference between patients receiving typical and atypical antipsychotics, although some opinions supporting that abnormalities in blood sugar may be higher with atypical than typical antipsychotic medications [2,3].

Another source also stated that although the mechanism of the effects of antipsychotic drugs on the incidence of glucose metabolism, especially the increase in blood glucose levels, is still uncertain [20] and the amount of research that is still controversial, but some experts are able to formulate a mechanism that may underlying these events, namely through a reduction in insulin sensitivity, increased insulin resistance and toxic effects of antipsychotics on beta cells [5,9].

The results of this study suggests that the tendency of beta cell dysfunction as one of the basic mechanisms of disease with type 2 diabetes, it occurs in individuals with longer use of haloperidol <1 year, through the toxic effects of antipsychotic haloperidol on beta cells, because respondents tend to decrease HOMA β. Where it is known that the examination HOMA β is one of the gold standard that has been widely recognized validity and reflect the pancreatic beta cell function accurately [21]. However, determination of cut-off point in this study cannot be done, because there is no control group. This becomes a limitation of the study, because there is no cut-off point value as a guide to determine the incidence of beta cell dysfunction.

Moreover, the tendency of hyperglycemia by HbA1c in patients with schizophrenia who use haloperidol in this study, probably due to beta cell dysfunction. Where we know that the beta cell dysfunction will decrease insulin secretion, thus decreasing cell glucose uptake, resulting in an increase in blood glucose levels, although there is no significant association. This was probably due therefore, all the samples used were inpatients, where food supply is limited, so it will affect the process of adaptation to patients with diet and amount of food in the hospital. According to Goldstein [22] that, onset of beta cell dysfunction, occurs before the development of hyperglycemia. At the time of diagnosis of diabetes, beta cell dysfunction may be decreased to 50%, so that interventions for the prevention or treatment of diabetes, is more effective at the beginning of the disease, as early detection of beta cell dysfunction to prevent further complications of type 2 diabetes.

Schizophrenic patients at high risk for development of type 2 diabetes, which is not dependent on the interaction between genetic and environmental factors. However, it was reported that over 50% of individuals with schizophrenia suffer from diabetes, of which 30% had a family history of type 2 diabetes. In addition, bad behavior such as unhealthy diet (high fat, low fiber, lack of exercise and smoking), contribute to the development of diabetes, which is associated with obesity [2].

For this reason, according to researchers, people with schizophrenia need treatment earlier, in an effort to prevent damage glucose tolerance, which can lead to type 2 diabetes. Although the study, the genetic history of diabetes difficult to obtain, because the difficulty researchers met with families of patients. However, there are some patients who are found to have a genetic history of diabetes, but still showed hyperglycemia and beta-cell dysfunction.

5. Conclusion

Based on the above explanation, it can be concluded as follows:

1. Patients with schizophrenia who use haloperidol, which is treated in RSKD Dadi, has been experiencing hyperglycemia (HbA1c> 5.5%). The longer the use of haloperidol higher HbA1c levels. Found 4.3% of hyperglycemia on the use of haloperidol <1 year, and 23.9% on the use of> 1 year.
2. The mechanism of occurrence of hyperglycemia in patients mentioned above, through the beta cell dysfunction. The longer the use of haloperidol, the lower the value of HOMA-β. Found 28.3% of beta cell dysfunction in the use of haloperidol <1 year, and 54.3% on the use of> 1 year. Beta cell dysfunction associated with the use of haloperidol old. The lower the value of HOMA-β, the higher levels of HbA1c. Hyperglycemia that occurs, associated with beta cell dysfunction.

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