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Insulin Therapy Increases the Risk of Hypokalemia and Arrhythmia in Diabetic Patients with Coronary Heart Disease: A Retrospective Study in Wahidin Sudirohusodo General Hospital

(*Terapi Insulin Meningkatkan Risiko Hipokalemia dan Aritmia pada Penderita Diabetes dengan Penyakit Jantung Koroner: Studi Retrospektif di RSU Wahidin Sudirohusodo*)

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ABSTRACT

Background: Cardiovascular disease is the most common cause of morbidity and mortality in diabetic patients. Patients with Diabetes Mellitus (DM) often require insulin therapy to control hyperglycemia, yet, it is associated with the risk of hypokalemia and dysrhythmia. **Objectives:** To evaluate the prevalence and the risk of hypokalemia and arrhythmia due to insulin therapy in DM patients with coronary heart disease (CHD) comorbidity. **Material and Methods:** The study was conducted retrospectively based on medical record data from January 2021 to December 2021 in Wahidin Sudirohusodo general hospital. The inclusion criteria include the out-hospital patients diagnosed with DM with CHD comorbidity. The patients were divided into 2 groups, those who received insulin and those who received oral antidiabetic drugs (OAD). Hypokalemia was defined if an electrolyte characterized by a low serum potassium concentration with a normal range of 3.5 – 5.0 mEq/L. Arrhythmia was defined if abnormal changes in a regular heartbeat, including an irregular heartbeat, a skipped heartbeat, a fast heart rate (tachycardia), or a slow heart rate (bradycardia). **Results:** The data were obtained from 322 patients' medical record, 161 was treated with insulin, and 161 received OAD. The insulin-treated patients had a significantly lower blood potassium level compared to the OAD group. The insulin group had 63,40% incidents of hypokalemia, while in the OAD group only 16,80% experienced hypokalemia ($p<0.05$). The presence of arrhythmia was detected in 63,40 % of insulin-treated patients, while only 29,80% had arrhythmia in the OAD group ($p<0,05$). **Conclusions:** Insulin Therapy in DM patients with coronary heart disease can increase the incidence of hypokalemia, which may result in arrhythmia in patients with coronary heart disease.

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ABSTRAK

Latar Belakang: Penyakit kardiovaskular merupakan penyebab paling umum morbiditas dan mortalitas pada pasien diabetes. Penderita Diabetes Mellitus (DM) seringkali membutuhkan terapi insulin untuk mengontrol hiperglikemia, namun hal ini berhubungan dengan risiko hipokalemia dan disritmia. **Tujuan:** Mengevaluasi prevalensi dan risiko hipokalemia dan aritmia akibat terapi insulin pada pasien DM dengan komorbiditas Penyakit Jantung Koroner (PJK). **Bahan dan Metode:** Penelitian dilakukan secara retrospektif berdasarkan data rekam medis dari Januari 2021 sampai Desember 2021 di RSU Wahidin Sudirohusodo. Kriteria inklusi meliputi pasien rawat jalan yang didiagnosis DM dengan komorbiditas PJK. Para pasien dibagi menjadi 2 kelompok, mereka yang menerima insulin dan mereka yang menerima obat antidiabetik oral (OAD). Hipokalemia didefinisikan jika elektrolit ditandai dengan konsentrasi kalium serum yang rendah dengan kisaran normal 3,5 – 5,0 mEq/L. Aritmia didefinisikan jika perubahan abnormal pada detak jantung yang teratur, termasuk detak jantung yang tidak teratur, detak jantung yang dilewati, detak jantung yang cepat (takikardia), atau detak jantung yang lambat (bradikardia). Hasil: Data diperoleh dari rekam medis 322 pasien, 161 dirawat dengan insulin, dan 161 menerima OAD. Pasien yang diobati dengan insulin memiliki kadar kalium darah yang secara signifikan lebih rendah dibandingkan dengan kelompok OAD. Kelompok insulin mengalami 63,40% kejadian hipokalemia, sedangkan pada kelompok OAD hanya 16,80% yang mengalami hipokalemia ($p<0,05$). Adanya aritmia terdeteksi pada 63,40 % pasien yang mendapat terapi insulin, sedangkan pada kelompok OAD hanya 29,80% yang mengalami aritmia ($p<0,05$). **Kesimpulan:** Terapi insulin pada pasien DM dengan penyakit jantung koroner dapat meningkatkan kejadian hipokalemia yang dapat mengakibatkan aritmia pada pasien penyakit jantung koroner.

Kata Kunci : Hipokalemia, Insulin, Aritmia, Diabetes mellitus, Penyakit jantung koroner

INTRODUCTION

Coronary heart disease (CHD) has claimed around 38% of deaths worldwide in 2019 (WHO, 2021). CHD occurs due to narrowing or blockage in the coronary blood vessel wall due to the deposition of fat and cholesterol, resulting in the blood supply to the heart being disrupted. According to American Heart Association data (2019), CHD affects at least 26 million people worldwide and is increasing. It is estimated that the prevalence of CHD in the United States is around 6.5 million (Dunlay et al., 2019). In Indonesia, cardiovascular disease ranks as the fourth cause of death after stroke, hypertension, and diabetes mellitus (DM). The incidence of heart disease based on Basic Health Research in South Sulawesi province is 1.46% (Indonesia Basic Health, 2019).

Epidemiological and prospective studies have observed the frequent coexistence between CHD and DM. Diabetes mellitus can trigger or worsen heart disease due to the accumulation of glycation end products, oxidative stress, inflammatory disorders, intracellular calcium build-up, and altered microRNA expression, not to mention the formation of atherosclerosis and coronary artery disease (Lehrke and Marx, 2017).

The treatment of DM often requires insulin. However, insulin can cause mild hypokalemia since it promotes the entry of potassium into skeletal muscle and liver cells by increasing the activity of the Na-K-ATPase pump. Increased epinephrine secretion due to insulin-induced hypoglycemia can also play a role in worsening hypokalemia. The majority of patients with diabetic ketoacidosis (DKA) with hyperosmolar and hyperglycemia (HHS) would experience potassium deficiency with an average

potassium deficit of 3-5 mEq/kg, but in some cases, it can exceed 10 mEq/kg. Several factors contributing to decreased potassium levels include vomiting, increased potassium loss due to osmotic diuresis and excretion of ketoacid anions, and loss of potassium from cells due to glycogenolysis and proteolysis. Therefore, insulin therapy may increase the risk of severe hypokalemia, especially in patients with normal or low serum potassium concentrations at hospital admission (Liamis, 2014).

Potassium deficiency (hypokalemia) can alter the function of several organs and most notably affect the cardiovascular system, neurological system, muscles, and kidneys. This condition can determine the mortality and morbidity of patients (Coregliano-Ring et al., 2022) The two main unwanted effects of hypokalemia are hypertension and ventricular arrhythmia. Research shows that potassium deficiency can increase blood pressure, and intravascular volume expansion, and may increase the effects of various neurohormonal hypertension. Hypokalemia can be a predisposing condition to the development of various ventricular arrhythmias including ventricular fibrillation (Coregliano-Ring et al., 2022). Hypokalemia also causes hyperpolarization and non-responsiveness of the membrane. If the potassium balance is disturbed, it can lead to disruption of the electrical conduction of the heart, dysrhythmias, and even sudden death (Kardalas et al., 2018).

Therefore, this study aimed to evaluate the level of risk of hypokalemia and arrhythmia in CHD patients who use insulin therapy to control hyperglycemia at the Integrated Heart Center, Wahidin Sudirohusodo Hospital, Makassar. This study is important to confirm the safety and risk of insulin use in coronary heart patients with diabetes mellitus.

MATERIAL AND METHODS

Study design and patient population

The study was conducted from September to December 2021 at the outpatient clinic of the Integrated Heart Centre of the Wahidin Sudirohusodo Makassar Center General Hospital. The study includes all CHD patients with DM treated either with insulin or oral antidiabetic (OAD) at Wahidin Sudirohusodo Hospital Makassar from 2020 through 2021. This study used a purposive sampling technique to determine certain criteria based on the research objectives and research problems. This research has received ethical approval issued by the health research ethics committee of the faculty of Medicine Unhas on July 26, 2021, under number 474/UN4.6.4.5.31/PP36/2021.

Data collection

Patients were divided into the INSULIN and OAD groups. The inclusion criteria were adult patients at the Integrated Cardiac Center who have diabetes mellitus and were prescribed insulin or oral hypoglycemics (comparative control). The patients should have normal potassium levels before

administration of antidiabetic or insulin therapy. The exclusion criteria Patients with significant comorbidities other than CHD, such as kidney disease. It was considered that patients with renal failure were excluded because they generally use diuretics that have a risk of hypokalemia such as furosemide which can cause a high risk of hypokalemia.

Data were obtained and collected from the patient's medical records, including the vital signs (heart rate, respiratory rate, systolic and diastolic blood pressure), serum potassium levels (K^+), fasting blood glucose levels, and electrocardiography (ECG) at the baseline and at after two months from treatment initiation.

Hypokalemia was defined if the electrolyte serum analysis showed serum potassium levels below the normal range of 3.5 – 5.0 mEq/L. The presence of arrhythmia was confirmed if abnormal changes were detected in ECG traces, including abnormal peaks, ventricular tachycardia, atrial fibrillation, heart block, or slow heart rate (bradycardia). The category of arrhythmias was determined by the cardiologist and vascular specialists. The vital signs were also monitored daily including the heart rate, respiratory rate, and systolic and diastolic blood pressures.

Statistical Analysis

All data were presented as Mean ± SD. The differences between variables before (pre) and after (post) treatments were analyzed using a paired t-test after determining the normal distribution of the data. A chi-square test was performed to determine whether the type of treatment affects the presence of hypokalemia and arrhythmia. If a p-value < 0.05 was obtained, the correlation was confirmed.

RESULTS AND DISCUSSION

Patient demography

The characteristics of the patients are depicted in Table 1. In general, DM patients with CHD were predominantly male, 64.60% in the OAD and 78.90 % in the insulin groups.

Table 1 Patient Demographics

	OAD		INSULIN	
	N	%	N	%
GENDER				
Male	104	64.60%	127	78.90%
Female	57	35.40%	34	21.10%
Result	161	100%	161	100%

AGE (YEAR)				
30 – 40	1	0.60%	6	3.70%
41 – 50	18	11.20%	27	16.80%
51 – 60	56	34.80%	68	42.20%
61 – 70	65	40.40%	56	34.80%
> 71	21	13.50%	4	2.50%
Result	161	100%	161	100%
BODY WEIGHT (Kg)				
40 - 60	37	23%	35	21.70%
61 - 80	105	65.20%	108	67.10%
> 81	19	11.80%	18	11.20%
Total	161	100%	161	100%

According to a previous report, men are more prone to developing CHD disease due to several risk factors that are more often found in males, including high blood pressure, obesity, smoking as well as an unbalanced lifestyle (Al-Nohair et al., 2020). Unlikely, women are bestowed with female hormones, especially estrogen, which also serves as a protective immunity. Estrogen can regulate the level and activity of ion channels and modulate the repolarization of the heart. This, in turn, leads to gender differences in calcium and potassium channel modulation, which may contribute to the lower number of CHD cases found in women's fields (Crescioli, 2021).

Potassium levels in patients treated with oral antidiabetic (OAD) and insulin

Table 2. Potassium levels in patients treated with oral antidiabetic (OAD) and insulin before and after 2 months of therapy.

Treatment	Potassium (K) mmol/L		
	Pre	Post	
	Mean ± SD	Mean ± SD	P (Value)
ODA	4.22 ± 0.417	4.1 ± 0.639	0.018
INSULIN	4.89 ± 0.892	3.45 ± 0.457	< 0.001
P (Value)	< 0,001	< 0,001	

As shown in Table 2, the average potassium levels in both groups decreased after receiving treatments for 2 months. However, the percentage of reduction of potassium levels in OAD patients was smaller,

approximately 2.8% from the baseline value. Meanwhile, in the insulin-treated patients, the mean potassium levels significantly dropped from 4.89 ± 0.892 to 3.45 ± 0.457 mmol/L, which is below the normal level. This shows that ODA consumption may cause a slight decrease in potassium levels, but since it occurred consistently in almost all patients, statistically, it resulted in a significant difference (P=0.018). This lower potassium level, from 4.22 ± 0.417 to 4.1 ± 0.639 mmol/L, did not have a clinical effect, since the decrease in potassium levels was still within the normal range (3.5-5.0 mmol/L). While in the patients receiving insulin treatment, there was a significant decrease in potassium levels of about 30% with a p-value of < 0.001 (very significant). This shows that the use of insulin increased the risk of hypokalemia after 2 months of use.

Table 3 Number and Percentage of Patients Who Develop Hypokalemia, Hyperkalemia, or Normokalemia After Treatment

Criteria	TYPES OF TREATMENT			
	OAD (N)	%	INSULIN (N)	%
Hypokalemia	27	16.80%	102	63.40%
Hyperkalemia	21	13.00%	0	0.00%
Normokalemia	113	70.20%	59	36.61%
Total	161	100%	161	100%

Chi-Square

$\chi 2$ Tests			
	Value	df	p
$\chi 2$	81.6	2	< 0.001
N	322		

The analysis of the occurrence of hyperkalemia or hypokalemia in patients after treatment can be seen in Table 3. The incidence of hypokalemia after insulin use was found in 63.40% of patients, and those with normokalemia were only 36.61%. In the OAD group, patients with hypokalemia were 16.80%, and patients with normal potassium levels were 70.20%. The result of the Chi-square analysis shows p<0.001, indicating that the choice of treatment, in this case, insulin administration, significantly influences the presence of hypokalemia in patients.

The use of insulin can cause a drop in blood potassium levels and potentially triggers hypokalemia. This incidence has previously been studied by Andersen et al. (2021). It is found that insulin treatment led to hypoglycemia in patients which coexisted with a significant decrease in serum potassium compared to the control group (Andersen et al., 2021). These results may relate to the mechanism of action of insulin, during which insulin promotes the entry of K^+ into skeletal muscle and liver cells by increasing the activity of the Na^+-K^+-ATPase pump, leading to insulin-induced hypokalemia (Liamis, 2014). Insulin therapy may lower the concentration of potassium directly or indirectly by reversing hyperglycemia. Therefore, insulin therapy can lead to severe hypokalemia, especially in patients with normal or lower serum potassium baseline levels (Liamis, 2014).

The risk of arrhythmias in patients treated with oral antidiabetic (OAD) and insulin

Arrhythmias is one of the clinical manifestations of hypokalemia that may result in fatal outcomes. In this study, the presence of arrhythmia is evaluated in the OAD and Insulin groups. As seen in Table 4, the percentage of patients who experienced arrhythmic events was significantly higher in the insulin than those in the OAD group (63.40% vs 29.80%). Using a Chi-square analysis, it is found that the p-value was < 0.001, showing a very significant correlation between the type of treatment given and the presence of an arrhythmia.

Table 4. The Number and Percentage of Patients Experienced Arrhythmias After 2-month Treatments

ECG examination	TYPES OF TREATMENT				Total
	OAD (N)	%	INSULIN (N)	%	
Arrhythmia	48	29.80%	102	63.40%	249 (46.6%)
Non-arrhythmia	113	70.20%	59	36.60%	73 (36.6%)
Total	161	100%	161	100%	322 (100%)

Chi-Square

$\chi 2$ Tests			
	Value	df	p
$\chi 2$	36.4	1	< 0.001
N	322		

These findings are also described in the study of Andersen et al. (2021). It was observed the insulin group was more prone to hypokalemia, and some cases resulted in an increased incidence of ventricular arrhythmias (Andersen et al., 2021). Two major adverse effects of hypokalemia affect the cardiovascular system, i.e. hypertension and ventricular arrhythmia. Hypokalemia can decrease cardiac repolarization, leading to the preservation of intracellular Ca^{2+} in the cardiomyocytes (Skogestad and Aronsen, 2018). Because of the inhibition of Na-K-ATPase action, hypokalemia potentially causes hyperpolarization and non-responsiveness of the membrane, resulting in a disruption of the electrical conduction of the heart, dysrhythmia, and even sudden death (Kardalas et al., 2018).

The comparison of blood fasting glucose (BFG) levels in patients treated with oral antidiabetic (OAD) and insulin

In this study, we also compared the effect of insulin and OAD treatment before and 2 months after the treatments (Table 5).

Table 5. The blood fasting glucose (BFG) levels Before and two months after treatment

Treatment	BFG RATE (mg/dL)		
	Pre (Mean ± SD)	Post (Mean ± SD)	P (Value)
OAD	188.27 ± 73.282	159.42 ± 55.787	< 0.001
INSULIN	284.67 ± 78.07	192.83 ± 67.42	< 0.001
P (Value)	< 0,001	< 0,001	

The BFG levels are found to be greatly different between the OAD and insulin groups, not only post-treatment but also in the pre-treatments. The BFG pre-treatment level in the OAD group was 188.27 ± 73.282 compared to the insulin group's 284.67 ± 78.07 mg/dl ($p<0.001$). The reason for this discrepancy is due to a higher BFG level requirement for the patients to initiate insulin therapy. It is stated in the guidelines, that to start insulin therapy, the BFG level is supposed to be above 250 mg/dL (Indonesian Society of Endocrinology, 2021). After administration of both OAD and insulin treatment, the BFG value decreased significantly (p-value < 0.001), but the percentage of reduction was much higher in the insulin group (33%), whereas for OAD the percentage of decrease was about 15%.

Insulin is a powerful anabolic hormone that exerts its metabolic effects primarily on the liver, adipose tissue, and skeletal muscle. Insulin increases fuel storage by (1) increasing glycogen synthesis in the liver and muscles, (2) increasing triglyceride synthesis and deposition in adipose tissue, and (3) increasing protein synthesis and inhibiting proteolysis. Insulin also increases glucose oxidation, providing an important source of energy in the form of ATP (Ormazabal et al., 2018). Biguanides are generally considered the drug of choice in obese type 2 diabetes. Metformin can be used with other

classes of oral antidiabetic drugs or insulin. Sulfonylureas' mechanism of action involves a direct secretory effect on the beta cells of the pancreatic islets. Adenosine triphosphate (ATP) sensitive potassium channels (K^+_{ATP}) of the pancreatic beta cells play an important role in the release of insulin and are composed of two components: the pore and the regulatory subunit (SUR-1) (Dahlén et al., 2022)

The comparison of vital signs in patients treated with oral antidiabetic (OAD) and insulin

The examination of vital signs in this study includes the heart rate, respiration rate, and systolic and diastolic blood pressure before and after 2 months of receiving OAD and insulin. This data can be seen in tables 6, 7, 8, and 9.

Table 6 Patient Heart Rate Before and After Treatment

Treatment	Heart Rate (bpm)		
	Pre (Mean ± SD)	Post (Mean ± SD)	P (Value)
OAD	76.72 ± 11.209	78.07 ± 12.094	0.259
INSULIN	77.26 ± 11.67	77.28 ± 11.51	0.989
P (Value)	0.672	0.549	

Table 7 Patient Respiration Rate (RR) Before and After Treatment

Treatment	Respiration Rate (respiration per minute)		
	Pre (Mean ± SD)	Post (Mean ± SD)	P (Value)
OAD	19.08± 17.21	19.03 ± 1.77	0.803
INSULIN	19.17 ± 11.67	19.2 ± 1.65	0.854
P (Value)	0.655	0.357	

Based on the results, the vital signs for heart and respiration rate (tables 6 and 7) have no significant relationship with the type of treatment received. The heart rate measurement data before insulin treatment was 77.26 ± 11.67 rpm and after treatment was 77.28 ± 11.51 rpm. The respiration rate pre-treatment was 19.17 ± 11.67 rpm and post-treatment was 19.2 ± 1.65 rpm. Both heart rate and respiration rate were in the normal range in both groups, where the standard limit for the heart rate is 60-80 bpm, and the normal limit for respiration rate is 12-20 rpm. From these data, it can be concluded that insulin use has no significant effect on the heart rate and respiration rate in CHD patients with diabetes mellitus comorbidity.

Nevertheless, previously Barbosa TC et al., (2018) reported that the administration of insulin can slightly increase the respiratory rate and the heart rate. This effect may derive from insulin stimulation on the carotid body-mediated hyperventilation in humans, where the carotid body contains chemoreceptors in type I glomus cells that detect chemical stimuli from arterial blood in the carotid sinus (Barbosa et al., 2018). However, this effect was not observed in the subjects of our study.

Table 8 Systolic Blood Pressure Before and After Treatment

Treatment	Systolic Blood Pressure (mmHg)		
	Pre Mean ± SD	Post Mean ± SD	P (Value)
OAD	132.27 ± 25.263	134.24 ± 31.968	0.544
INSULIN	133.57 ± 28.21	134.89 ± 28.09	0.672
P (Value)	0.662	0.845	

Table 9 Diastolic Blood Pressure Before and After Treatment

Treatment	Diastolic Blood Pressure (mmHg)		
	Pre (Mean ± SD)	Post (Mean ± SD)	P (Value)
OAD	84.56 ± 76,924	76.37 ± 10.956	0.187
INSULIN	76.72 ± 28.21	79.98 ± 56.91	0.955
P (Value)	0.996	0.431	

Similar to the respiratory and heart rate, there was no significant difference found between the OAD and Insulin groups in systolic and diastolic blood pressures. The systolic blood pressure before and after receiving insulin was 133.57 ± 28.21 mmHg and 134.89 ± 28.0 mmHg, respectively. Whereas, the diastolic blood pressure was 76.72 ± 28.21 and 79.98 ± 56.9 mmHg, respectively. This means that the insulin treatment did not significantly affect the patient's blood pressure. Insulin might affect blood pressure since it may affect activation of the sympathetic nervous system, renal reabsorption of sodium, and cause an alteration of the transmembrane ion transport, as well as resistant vascular hypertrophy (Mancusi et al., 2020; Zhou et al., 2014). Previously, a study reported that the use of insulin can cause an increase in blood pressure in type 2 DM patients (Tsimihodimos et al., 2018). Nonetheless, these effects were not observed in our study. It is assumed that the insulin stimulation on blood pressure is progressive and may not observe in our study because the duration of treatment is only 2 months.

CONCLUSION

The use of insulin in patients with coronary heart disease can increase the risk of hypokalemia. The coexistence of insulin treatment and hypokalemia may result in a substantial risk of triggering arrhythmias. However, insulin treatment was not found to increase the risk of hypertension in this population. The result of this study may necessitate close monitoring of patients' potassium levels during insulin therapy to prevent adverse cardiovascular events in coronary heart disease patients.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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