SYSTEMATIC REVIEW

Medication Adherence in Type 2 Diabetes Mellitus Patients with Coronary Heart Disease

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ABSTRACT

Background: Diabetes medication non-adherence can aggravate the patient's condition and raise the chance of acquiring diabetes complications such as coronary heart disease. Medication adherence can help prevent micro- and macrovascular problems. Objective: This study aimed to investigate the medication adherence of type 2 diabetic patients with coronary heart disease. Material and Method: This research used a systematic literature review for the research design, with a PRISMA chart as a guideline. Researchers searched 3 databases using predefined keywords: PubMed, Google Scholar, and ScienceDirect. Result: The search yielded 3,373 pieces of literature, and six pieces that fit the requirements were chosen. The total number of people who responded was 9,950. More men over 60 years old who have had diabetes for more than 5 years, who are taking oral medication, insulin, or combination treatment, and who are ex-smokers were shown to have characteristics of people with type 2 diabetes mellitus and coronary heart disease. Results from a systematic literature review revealed five kinds of literature with low medication adherence levels and one literature with a high medication adherence rate. Conclusion: Medication adherence differs among type 2 diabetic patients with coronary heart disease. More research, however, has revealed that the level of medication adherence in type 2 diabetic patients with coronary heart disease remains low.

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Highlights

1. Type 2 diabetes mellitus (T2DM) that is not appropriately handled can result in macro- or micro-complications.
2. Medication adherence is one of the most important efforts to do to prevent complications in chronic diseases such as T2DM.
BACKGROUND

Diabetes mellitus (DM) is a chronic condition that remains a serious health issue in Indonesia. Diabetes mellitus is a metabolic condition characterized by hyperglycemia caused by defects in insulin secretion, action, or both (Saputi, 2020). Polydipsia, polyuria, polyphagia, weight loss, and tingling are all symptoms of diabetes mellitus. Diabetes mellitus that is not handled properly can lead to various chronic complications, namely vascular complications, one of which is coronary heart disease (Fatimah, 2015; Aquarista, 2017). Coronary heart disease (CHD) is characterized by a lack of blood and oxygen delivery to the myocardium. It is caused by a blockage of the coronary arteries and an inappropriate oxygen supply. It usually involves plaque formation in the coronary arteries' lumen that blocks blood flow (Shahjehan & Bhutta, 2023).

The prevalence of CHD in Type 2 diabetes mellitus (T2DM) patients is very complex. It is linked to atherosclerosis and influenced by various variables such as hypertension, hyperglycemia, dyslipidemia, smoking, family history of CHD, and obesity (Yuliani, et al., 2014). About 75% of T2DM patients die from cardiovascular disease, including CHD. In T2DM patients, CHD is more likely to be a complex disease characterized by a small disease, diffuse calcification, and multivessel disease (Naito & Miyauchi, 2017). Pathophysiological changes occur in T2DM patients, such as thickening of the capillary basement membrane and coronary arteries. In addition, hyperglycemia also occurs, which causes an increase in type IV hyperlipidemia, triglycerides, and abnormal platelet formation, thereby increasing cholesterol and triglyceride levels and causing atherosclerosis, which is the basic pathophysiology of CHD. Diabetes self-management education, such as patient compliance in managing diet, is critical to avoid acute problems and lower the chance of long-term complications such as CHD (Aquarista, 2017; Hestiana, 2017; American Diabetes Association, 2020).

Medication adherence is the extent to which a person takes medication, follows a diet, or makes lifestyle adjustments per a healthcare provider's agreed-upon recommendations. For measuring adherence, ideal tools would be needed. Measurement that is user-friendly, low-cost, easy to carry, highly reliable, practical, and flexible. However, there is no single questionnaire measurement that can meet all the gold standards since each has its own perks (Saibi, et al., 2020; Lam & Fresco, 2015). One of the questionnaires that are used for this research is the Morisky Medication Adherence Scale (MMAS)-8 questionnaire, which can measure drug medication adherence. The questionnaire assesses medication adherence in patients with chronic diseases, including diabetes, which the WHO has validated. Medication non-adherence might result in difficulties, hospitalization, and significant costs. Other questionnaire measurements like PBS, MDAM, MTR-7, and others were also validated by other research or the country where the study was conducted (Nanda, et al., 2018).

OBJECTIVE

This study aimed to investigate the medication adherence of type 2 diabetic patients with CHD. From this review, it is hoped that T2DM patients can pay more attention to and improve medication adherence in DM therapy to prevent complications.

MATERIAL AND METHOD

Study design
This systematic review method was performed to assess the level of medication adherence in T2DM patients with coronary heart disease. The PRISMA checklist in Figure 1 was used in the protocol and evaluation of the systematic review to figure out the selection of studies that had been located and were suited to the objectives of the systematic review (Nursalam, 2020).

Search strategy
The initial step was to identify the literature by entering keywords ("type 2 diabetes" OR "diabetes mellitus" OR "Diabetes Mellitus type 2") AND ("coronary heart disease" OR "coronary artery disease" OR "acute coronary syndrome") AND ("medication adherence" OR "treatment adherence" OR "medication maintenance") to a predetermined database, the PubMed, Scopus, and ScienceDirect.
Selection criteria and methodologic quality assessment

Inclusion criteria for this study included: 1) a cross-sectional study over 10 years, 2012-2022, 2) literature in Indonesian or English; and 3) availability in a full-text article. Meanwhile, the exclusion criteria in this study included 1) inaccessible literature; 2) Literature that did not describe medication adherence.

The PICO (Patients, Intervention, Comparators, Outcomes) approach was used in this study. The patients were Type 2 Diabetes Mellitus patients. The intervention was medication adherence, while the comparators were not applied. The outcomes included the increased risk of coronary heart disease.

The literature was screened based on its title and abstract and then sought for retrieval. Literature that did not discuss medication adherence in T2DM patients with CHD was excluded. Literature that meets the requirements was regarded as eligible. Eligible literature were assessed using the Newcastle-Ottawa Scale.

Data extraction

The authors extracted data from all the retrieved studies and evaluated their quality using full-text articles. If there were differences of opinion, the authors would check and discuss them with each other. The authors, the publication year, study location, research design, sample size, population characteristics, medication adherence instruments, and the level of medication adherence in the study were among the data picked.

RESULT

The PRISMA guidelines were used for the procedure and evaluation of the systematic review, as shown in Figure 1. The results obtained from three databases covered 3,383 kinds of literature. Researchers excluded 914 kinds of literature not from the years 2012-2022, 9 not in Indonesian and English, and 142 duplicates were removed. The initial screening stage was to determine studies with appropriate titles and abstracts. After the screening, 2,307 studies were excluded, leaving 11 relevant pieces of literature based on population. After all the literature was accessed to get the free full-text of the literature and analyzed, the researcher found that two pieces of literature could not be accessed, and three pieces of literature did not discuss the medication adherence of T2DM patients with CHD, so they were excluded. Six pieces of literature were chosen for this study.

All selected literature was assessed for quality with the NOS (Newcastle-Ottawa Scale) by answering screening questions relevant to the research questions, and some data provided answers to the research questions. Then each piece of literature answered seven questions according to the NOS scheme, adapted to cross-sectional studies. The results of the quality literature assessment can be seen in Table 1. From assessing the six literature using the Newcastle-Ottawa Scale adapted for cross-sectional study, we obtained a very good study from all the literature.
Table 1. Literature quality assessment.

<table>
<thead>
<tr>
<th>No</th>
<th>Authors (year)</th>
<th>NOS score</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afroz, et al., (2019)</td>
<td>9</td>
<td>Very good</td>
</tr>
<tr>
<td>3</td>
<td>Alatawi, et al., (2016)</td>
<td>9</td>
<td>Very good</td>
</tr>
<tr>
<td>4</td>
<td>Munkhaugen, et al., (2018)</td>
<td>9</td>
<td>Very good</td>
</tr>
<tr>
<td>5</td>
<td>Malik, et al., (2013)</td>
<td>9</td>
<td>Very good</td>
</tr>
</tbody>
</table>

Table 2 discusses the characteristics of the literature used in this systematic review, including the author's name, year of publication, background of the research place, research design, and number of samples. Of the six studies in the literature, several studies have different research locations, publication years ranging from 2013 to 2020, and samples ranging from 220 patients to a maximum of 3,536 samples.
Medication adherence in T2DM patients with CHD from the results of the six literature studies that have been selected is described in Table 3. Research by Afroz, et al., (2019) found that treatment compliance in T2DM patients with CHD was 27% compliant, and 32.5% were not compliant with treatment. This study showed that 14.8% of respondents had macrovascular complications, 20.7% had microvascular complications, and 27.9% had both complications. A p-value of 0.041 was obtained. Research by Sánchez-Hernández, et al., (2020) showed good medication adherence in patients with T2DM, with the percentage of patients adhering to their treatment as much as 66.2% and patients who were not adherent as much as 33.8%.

The study by Alatawi, et al., (2016) obtained results from MTR-7, which showed that 47% did not take their medication as recommended for one or more days in the previous week. For the MDAM results, approximately 27% did not take the prescribed number of dosages daily, 59% did not take them numerous times daily, and 50% did not take their prescription at predetermined time intervals between doses. MDAM and MTR-7 summary scores were significantly correlated with a p-value <0.001. The study by Munkhaugen, et al., (2018) had results with low Morisky scores (Score: >2 on the 8-item Morisky medication adherence questionnaire, indicating low adherence) of 9.6%, or 22 people out of 243 patients, for a p-value of 0.01.

Research by Malik, et al., (2013) found that non-compliance was higher in patients with high complexity compared to those with low complexity, with a percentage of 83.5% and 43.3%, respectively, thus getting a p-value <0.001. However, it was also found that patients with a history of CHD reported fewer adherence issues than those without a history of CHD, with 59.3% and 69.3%, respectively, resulting in a p-value <0.01. Research by Alramadan, et al., (2019) obtained results showing medication adherence in T2DM patients with CHD, with a percentage of patients who had low adherence of 17.9%, moderate adherence of 13.7%, and patients with high adherence levels of 18.8%, thus obtaining a p-value of 0.119.

Table 3. The level of medication adherence in type 2 diabetes mellitus patients with coronary heart disease.

<table>
<thead>
<tr>
<th>No</th>
<th>Authors (year)</th>
<th>Medication adherence instrument</th>
<th>Level of medication adherence</th>
<th>Total/p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afroz, et al., (2019)</td>
<td>Face-to-face interview using a structured questionnaire in a secure web-based application</td>
<td>Adequate 27% Inadequate 32.5%</td>
<td>P = 0.041</td>
</tr>
<tr>
<td>2</td>
<td>Sánchez-Hernández, et al., (2020)</td>
<td>MMAS-4 Questionnaire</td>
<td>Adherent 66.2% Non-adherent 33.8%</td>
<td>N = 3259</td>
</tr>
<tr>
<td>3</td>
<td>Alatawi, et al., (2016)</td>
<td>MDAM</td>
<td>A correct number of pills: Adherent 73% Non-adherent 27% The right time of day: Adherent 50% Non-adherent 50% The number of times to take the correct medication: Adherent 41% Non-adherent 59%</td>
<td>P &lt;0.001</td>
</tr>
</tbody>
</table>
MTR-7
The number of days without a dosage missed:
Adherent 53%
Non-adherent 47%

<table>
<thead>
<tr>
<th></th>
<th>Munkhaugen, et al., (2018)</th>
<th>MMAS-8 Questionnaire</th>
<th>Low Morisky score 9.6%</th>
<th>P = 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Malik, et al., (2013)</td>
<td>51-item potential for benefits scale</td>
<td>Low complexity patients 43.3%</td>
<td>P = &lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medium complexity patients 70%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High complexity patients 83.5%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>CHD 59.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without CHD 69.3%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Alramadan, et al., (2019)</td>
<td>MMAS Questionnaire</td>
<td>Low 17.9%</td>
<td>P = 0.119</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medium 13.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High 18.8%</td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

Characteristics of research subjects in type 2 DM patients with coronary heart disease

In the five pieces of research literature obtained, the results of the characteristics of T2DM patients with CHD mostly come from the age group above 60 years with a percentage, except for one study belonging to Alatawi, et al., (2016), which shows the average age group of respondents under 60 years. In all studies, the most common gender in the study subjects was male, and the education level of most respondents was only a primary education level. The duration of suffering from DM in research subjects averaged more than 5 years, except for the respondent in Sánchez-Hernández, et al., (2020) who had respondents with DM duration of fewer than 5 years. In their research, Afroz et al., (2019) and Sánchez-Hernández, et al., (2020) showed that patients older than 60 years and with a longer duration of DM had an increased risk of 1.6 and 1.5 times higher of getting macro-vascular complications such as CHD and DM. Patients who smoke or have smoked also increase their risk of developing CHD by 1.5 times, which explains why the long duration of DM had worsened the patient's HbA1C. Among the patients' treatment modalities, it was also found that patients who used a combination of oral drugs and insulin had a higher prevalence of developing CHD. In comparison, patients who only used insulin had a higher prevalence of getting diabetic foot.

In the research by Sánchez-Hernández, et al., (2020) and Alatawi, et al., (2016), more respondents used oral medication therapy only. However, in the study by Afroz et al., (2019), many respondents used a combination treatment of oral medication and insulin, while in the study by Alramadan, et al., (2019) many respondents only used insulin treatment. Many subjects in the studies by Sánchez-Hernández, et al., (2020) and Alramadan, et al., (2019) lived in rural areas and were formerly active smokers; while, on the other hand, the subjects in the study by Afroz et al., (2019) lived more in urban areas, and many of them were active smokers.

The research by Alramadan, et al., (2019) explained that diabetes mellitus is a progressive disease where a longer duration of the disease will worsen pancreatic function, especially when there is long-lasting hyperglycemia. This study also showed that a diabetes duration of more than 10 years was an independent predictor of CHD and renal impairment. This study also explains that patients with a family history of DM will have an earlier risk of developing DM than those without. Hypertension and obesity also increase the risk of CHD by 3.4 and 1.7 times, respectively. CHD complications are also higher in male patients. It was also explained that using insulin medication or a combination of oral and insulin increased the risk of CHD by 2.2 and 1.9 times, respectively.

Level of medication adherence of type 2 diabetes mellitus patients with coronary heart disease

Adherence is a difficult behavior to quantify and evaluate, and its measurement does not have a gold standard. Each of these studies uses self-reported questionnaires validated by other studies or the country where this research was conducted.

In this study, we found that the majority percentage of treatment adherence among respondents was low. This study explained that the increasing age of DM patients would make them less adherent to their treatment. It was also found that increasing age in DM patients will increase the risk for microvascular or macrovascular complications. Only in the research of Sánchez-Hernández, et al.,
the percentage of treatment compliance in DM patients was high, which is different from other research studies. In this study, it was found that many of the respondents had a shorter duration of DM (<5 years), and the majority of respondents in this study had never smoked. It differs from other studies, which had active or former smokers as respondents. This study also had a percentage of patients using oral drugs at 63.2%, insulin at 11.4%, and a combination of oral and insulin at 9.5%. Some of these are factors that can affect medication adherence in patients. While other five studies obtained the results of low medication adherence in respondents and revealed that non-compliance in patients is generally due to the increasing number of drugs that must be consumed, many of the patients forget to take their medicine. Furthermore, it also explains that patients with low compliance can have a higher risk of complications. This study also found that the adherence rate of patients with T2DM who did not have CHD was lower than that of patients who had CHD. This study also mentioned that the repercussions of non-adherence to medicine are severe. In up to 50% of chronic diseases, treatment failures result in the progression of the illness, functional impairment, hospitalization, and death. This study also explains that a high level of education will indirectly encourage healthy living behaviors and a positive attitude toward health and disease prevention.

The research results on treatment compliance of T2DM patients with CHD obtained five pieces of literature that showed a low level of treatment compliance, and only research belonging to Sánchez-Hernández, et al., (2020) showed a high level of treatment compliance. So it can be concluded that the level of treatment compliance in T2DM patients with CHD still needs to be improved in the future.

Non-adherence with blood glucose-lowering or lipid-lowering drugs is connected with increased HbA1c and cholesterol levels, making adherence to recommended medications critical for metabolic control. For effective diabetes care, an accurate assessment of medication adherence is required. There is, however, no gold standard for such evaluation, even though many approaches have been published in the literature (Wabe, et al., 2011). The causes of non-adherence vary widely, including drug regimen, behavior, drug cost, age, low social support, and cognitive problems (Alfian, 2015). Efforts made to increase public knowledge of the importance of medication adherence include pharmaceutical therapy programs that need to be provided along with dietary management and physical exercise consisting of oral and injectable drugs (Soelistijo, et al., 2021). Positive family and social support are also important factors in diabetes management. Having family members participate in diabetes self-care activities is also recommended, including being physically active, eating healthy food, monitoring blood glucose, and adhering to medications (Bussell, et al., 2017).

**Strength and limitations**

This study discusses the level of medication adherence of T2DM patients with CHD, which is expected to educate patients so that they can pay more attention and improve medication adherence in DM therapy to prevent complications. However, this review has several shortcomings that make it less representative of the research on the level of medication adherence in T2DM patients with CHD. It could be due to the need for studies examining this issue. It could also be due to authors’ errors, which could contain elements of bias, both when searching the literature and when selecting and analyzing the results of the studies that have been collected.

**CONCLUSION**

The characteristics of T2DM patients with CHD are that they were mostly male, over 60 years old, and had suffered from DM for more than 5 years. Most lived in rural areas with low education and used oral treatment, insulin only, or a combination of oral and insulin. Medication adherence differs among T2DM patients with CHD. More research, however, has revealed that the level of medication adherence in T2DM patients with CHD remains low. It is hoped that T2DM patients can pay more attention and improve medication adherence in DM therapy to prevent complications.

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Author Contribution
SME contributes to analysis and interpretation of the data, drafting of the article, provision of study materials or patients, and data collection and assembly of data. SWM contributes to conception and design, critical revision of the article for important intellectual content, final approval of the article, statistical expertise, administrative, and technical, or logistic support. A contributes to critical revision of the article for important intellectual content, final approval of the article, statistical expertise, and administrative, technical, or logistic support. HN contributes to critical revision of the article for important intellectual content, final approval of the article, statistical expertise, and administrative, technical, or logistic support.

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