Annals of R.S.C.B., ISSN:1583-6258, Vol.28, Issue1, 2024 Pages: 485 - 498

Received 30 July 2024; Accepted 15 August 2024

Pathological Effects and Management Protocols of Diabetes Mellitus

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Abstract

Diabetes Mellitus (DM) is a chronic metabolic disease which manifested with low insulin production as well as insulin resistance resulting from genetic and environmental factors. It is one of the most rapidly growing diseases globally and poses a primary risk to global health. Over the past 30 years, the world has shown a continuous elevation in incidence of DM; especially in developing countries with the fastest growth in North Africa and the Middle East have the second maximum rate of diabetes. In T1DM, the individual body is no longer making insulin or in enough amount because the immune system has destructed and destroyed the pancreatic beta cells responsible for making the insulin. The exact reason for this pattern of diabetes is unrevealed, and almost all persons who experience this chronic illness do not realize how to manage it. T2DM is one of most prevalent diseases consisting of about 90–95% of all diabetes cases. T2DM is becoming more commonplace because of the excess obesity in the population. T2DM patients are mainly characterized as being overweight or existence of greater amount of body fats that mostly found in abdomen, at which situation, several inflammatory mechanisms, fatty substance elevates insulin resistance, for instance, free fatty acids delivered with adipocyte disorganizing. Primary driver for epidemically prevalence of T2DM is a worldwide elevation in obesity, style way of living, high-calorie food, and ageing of individuals. Interactions between risk factors and genetic inheritance are complicated to cause T2DM, such as obesity and sedentary lifestyle, hypo insulin secretion, increased lipolysis, and increased reabsorption of glucose from the kidney, and dysregulated glucose uptake, neurotransmitter imbalance, and increased production of liver glucose. Achieving good metabolic control and long-term maintenance of diabetes requires a combination of lifestyle changes and medications are necessary to achieving near-normal hemoglobin glycosides significantly and risk of macrovascular and microvascular problems will decrease

Keywords: T1DM, T2DM, Nephropathy, Retinopathy, Macrovascular disorders, Microvascular disorders

Background

Diabetes Mellitus (DM) is a chronic metabolic disease which manifested with low insulin production as well as insulin resistance resulting from genetic and environmental factors. It is one of the most rapidly growing diseases globally and poses a primary risk to global health. The disease could result in frequent damages and dysfunctions for different organs particularly nerve, blood vessel, kidney, heart and eye (Al-Shaeli et al., 2022; Zhao et al., 2023).

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Epidemiology

There was a rapid elevation in prevalence of disease at an alarming rate and was reported epidemically in 21st century, to affect millions of individuals around the world. As stated by the International Diabetes Federation (IDF). It is assumed that during 2019, 463 million people between 20-79 years were vivid with DM and expected to skip 640 million in 2040. Nearly fifty percent of patient's number with diabetes are insensible of their illness, thus, leading to developing diabetic complications; 5 million deaths approximately in 2015 were attributed to diabetes; the new manifest shows that DM persists to be a significant international health challenge and is likely to continue to go on growing basically in the following decades, which may have main implications for healthcare expenses, especially in developing world (Saeedi et al., 2019; Al-Sarray and Al-Shaeli, 2022; Al-Shaeli et al., 2022). Over the past 30 years, the world has shown a continuous elevation in incidence of DM, especially in developing countries with the fastest growth (Al-Shaeli and Ethaeb, 2019). Within IDF regions, North Africa and the Middle East have the second maximum rate of diabetes and 9.2% prevalence (El-Kebbi et al., 2021). The IDF reported that the Kingdom of Saudi Arabia (KSA) was in the middle first ten countries among peak spread averages of disease worldwide. The current prevalence of DM in KSA is around 23% (Al Dawish et al., 2016). The IDF reported that approximately one in four adults in Saudi Arabia would have Diabetes by 2045. There has been a lifestyle alteration among Saudi Arabian people related to urbanization and eating habits. The continuous exhaustion of big fat diets, great energy, and minimum scales of physical occupation drive alterations in energy equilibrium with preserving excess energies as fats since large quantities of energy consuming stimulate resistance to insulin prior the occurrence of apparent weight gains (Al-Shaeli and Ethaeb, 2019; Alemany, 2024).

In Iran, DM spreading in people of 25–70 years was determined at 11.9% in 2011, which manifests a rise of 36% compared to 2005 (Arokiasamy et al., 2021). It is appreciated that in the year 2031, nearly 9.3 million Iranians will likely experience the disease. As claimed by IDF in 2013, the prevalence in turkey was evaluated as 14.85% (Yıldırım and Marakoğlu, 2018). The development of obesity and the ageing of the population have been suggested as primary causes of DM epidemic. The prevalence in Iraq rated 8.5% to 13.9%, with around 1.4 million Iraqis having DM; the majority of Diabetes in Basra, Iraq, is very high, affecting one in five adults (Farmanfarma et al., 2020).

Classification

The disease can be categorized to four types**:**

1. Type 1 diabetes (T1DM) caused by the destruction of autoimmune- β-cells that absolutely reduces insulin production.

2. Type 2 diabetes (T2DM) caused by the loss of β -cells, and insulin excretion is significantly affected by the setting of insulin resistance.

3. Gestational diabetes mellitus is diagnosed during pregnancy and was not noted before gestation**.**

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4. Certain types of diabetes as a result of different causes, for instance, monogenetic diabetes syndromes, like diabetes of the neonatal, diabetes onset in young adults, exocrine pancreatic diseases (including pancreatitis and cystic fibrosis), and drug or chemically-stimulating DM like utilization the glucocorticoids or subsequently to transplantation of organs).

T1DM

A chronic illness featured by absolute insulin deficiency due to loss of β-cells in the pancreas and resulting in hyperglycemia (Wilcox et al., 2016; AL-Shaeli et al., 2022). Also recognized is diabetes of autoimmunity. Although the lifetime of symptoms onset is usually during childhood or adolescence, the symptoms may arise later (Gharban et al., 2023). In T1DM, the individual body is no longer making insulin or in enough amount because the immune system has destructed and destroyed the pancreatic beta cells responsible for making the insulin. The exact reason for this pattern of diabetes is unrevealed, and almost all persons who experience this chronic illness do not realize how to manage it (Szablewski, 2014). Novel accession for insulin treatment, for instance, insulin pumps, progress glucose evaluation, and mixture closed-loop devices, are in development (Forlenza et al., 2022).

T2DM

It is one of almost general metabolic illnesses globally (Hameed et al., 2015). A combination of two factors that primarily lead to its development: deficient in secretion of insulin through the β-cells of pancreas with disability of tissue to be sensitive for insulin cause an impairment in secretion of insulin and increasing the are the primary defects accountable for the development of the disorder (Sarkar et al., 2019). T2DM is one of most prevalent diseases consisting of about 90–95% of all diabetes cases. T2DM is becoming more commonplace because of the excess obesity in the population. T2DM patients are mainly characterized as being overweight or existence of greater amount of body fats that mostly found in abdomen, at which situation, several inflammatory mechanisms, fatty substance elevates insulin resistance, for instance, free fatty acids (FFAs) delivered with adipocyte disorganizing. Primary driver for epidemically prevalence of T2DM is a worldwide elevation in obesity, style way of living, high-calorie food, and ageing of individuals (Dilworth et al., 2021; Al-Hetty et al., 2023). This disease has an exception for rapidly growing over following 2 decades later; >70% of the diseased individuals will manifest in developed regions, mostly who aged 45-64 years; advanced age, even though it is a risk factor for T2DM, higher rate of children overweight can result in great widespread of disease in teenager and adolescent. It is an acute onset of an epidemic and a new public health problem of significant proportions (Kharroubi and Darwish, 2015; Saleem et al., 2021).

Clinical Presentation

DM is a variable disease that clinically presenting different symptoms. Children with T1DM typically develop the signs of polydipsia/ polyuria, as well as ketoacidosis in about 33% of patients (Syed, 2022). In adults, an appearance of T1DM might be varied or being found without classical signs observed in younger ones. Sometimes, T2DM people may develop diabetic ketoacidosis, especially ethnic minorities), (American Diabetes Association, 2014).

Received 30 July 2024; Accepted 15 August 2024

Classical signs of DM involved mainly hyperphagia, polydipsia and polyuria which occur commonly in T1DM, and revealed a rapid progressing for severely hyperglycemic condition with very high levels of hyperglycemia in T2DM (Adinortey, 2017). Extreme weight dropping is only general in T1DM or if T2DM remains undetected for a prolonged period. Unexplained weight loss, fatigue and body aches are also general signs of undiscovered diabetes (Baynes, 2015; Choudhury and Rajeswari, 2022). Symptoms that are mild or develop gradually can also go unnoticed. The symptoms of T1DM and T2DM are similar; however, these symptoms differed in their severity, rapidly developing to T1DM with more typically signs. T1DM some signs comprise weight dropping, urination, fatigue, candidiasis and blurred vision. Macrovascular and microvascular disorders can occur in patients who sensitive to long-lasting T1DM, which including peripheral vascular, heart, and coronary artery disorders (Psoma et al., 2024).

Diagnosis

Identifying diabetic patient through investigation can allow to earliest therapy and more obviously lowering the rate of complication in future. Also, diseased individuals at higher risks such as obese, hypertensive and families with a DM history must be examined frequently (Forbes and Cooper, 2013). Microvascular complications are found in about a quarter of patients with T2DM already having an exact period for diagnosing to indicate their experiences for DM > 5 years (Arnold et al., 2022). As a result, there are various ways of diagnosing Diabetes among individuals. DM can be diagnosed depending on glycosylated hemoglobin (HbA1c) level or plasma glucose level, including two-hour plasma level of glucose (2-h PG) value after 75 gram of oral glucose tolerance test (OGTT) as well as the fasting plasma glucose (FPG), (Karnchanasorn et al., 2016).

Pathogenesis of T2DM

Interactions between risk factors and genetic inheritance are complicated to cause T2DM, such as obesity and sedentary lifestyle, hypo insulin secretion, increased lipolysis, and increased reabsorption of glucose from the kidney, and dysregulated glucose uptake, neurotransmitter imbalance, and increased production of liver glucose (Wu et al., 2014; Galicia-Garcia et al., 2020). Glucagon secretion is a metabolic abnormality reported in hyperglycemia and T2DM (Hædersdal et al., 2023). At an early stage of disease, glucose tolerance could still normally although resistance to insulin due to compensatory over-secretion of insulin by pancreatic islets (Rutter et al., 2015). Eventually, there is impaired glucose tolerance resulting in increased post-prandial glucose (Jarvis et al., 2023). After which, there is a reduction in insulin production which leads to fasting hyperglycemia and the increased production of glucagon (Færch et al., 2016). Insulin resistance (IR) is a status characterized by diminished insulin action in objective tissues, which causes β-cells of the pancreas to carry on producing excess insulin, eventually causing its dysfunction through oxidative stress (Newsholme et al., 2019; Rahman et al., 2021). A shortage of tissue response to insulin leads to transient and unexpected hyperglycemia and high insulin levels, along with an inflammatory sign predisposing the person to metabolic syndrome and T2DM (Corkey et al., 2021). IR is a note of gaining weight and a sedentary way of living caused by excess energy consumption, low exercise and some genetic factors (Verdú et al., 2021). The liver

Annals of R.S.C.B., ISSN:1583-6258, Vol.28, Issue1, 2024 Pages: 485 - 498

Received 30 July 2024; Accepted 15 August 2024

performs a unique role in glucose metabolism, which is essential for systemic glucose homeostasis (Watt et al., 2019). The tissue pathophysiology of T2DM was detailed as following (Figure 1).

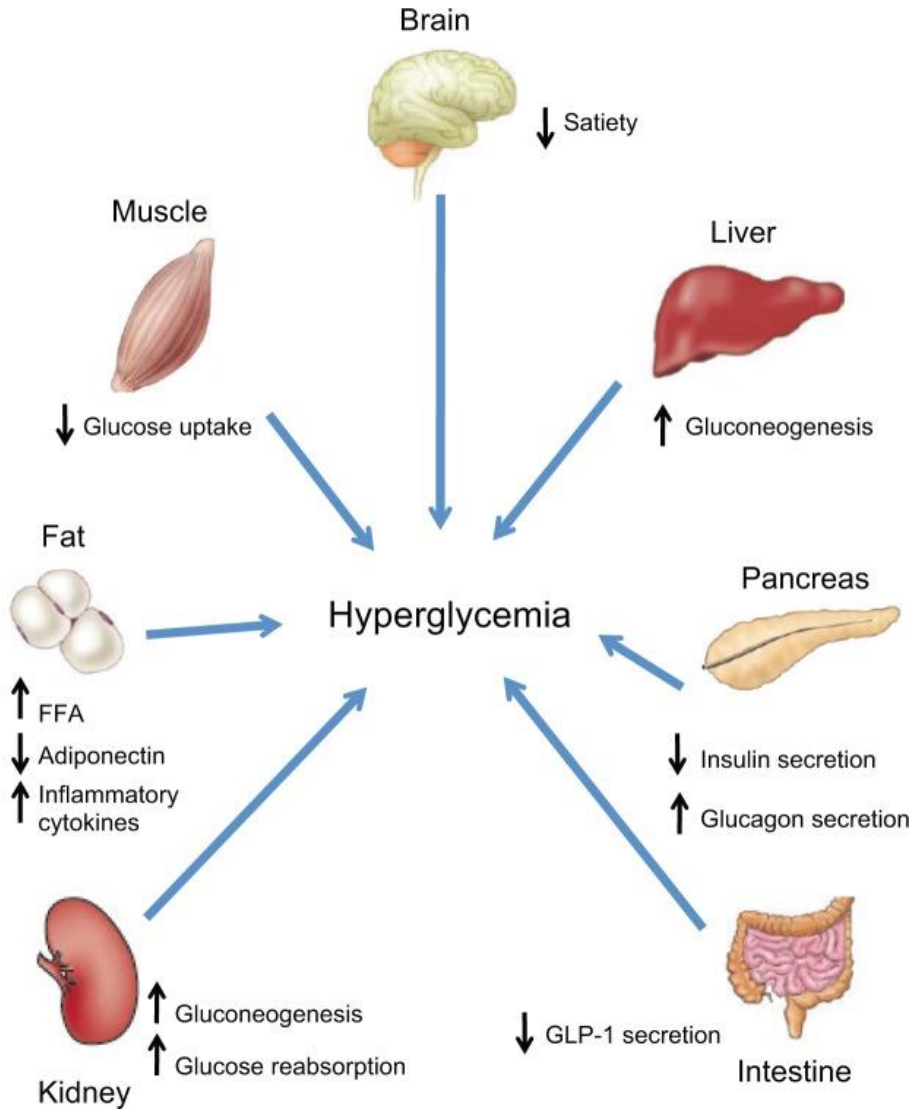

Figure (1): Pathophysiology of T2DM

Risk Factors

Environmental, metabolic and genetic are a complicated combination of risk factors for T2DM interacts with each other, affecting its prevalence and contributing to the actual development of the disease (Tremblay and Hamet, 2019). Genetics, environment, lack of exercise, lack of exercise, smoking, alcohol intake, dyslipidemia, desensitization of beta cells, high insulin levels and glucagon activity are the major risk factors of prediabetes and DM development (Alam et al., 2021). These factors are playing a significant impact on insulin resistance, insulin dysfunction and contribute for advancing of DM. However, individuals who are susceptible to diabetes due to fixed risk factors (race, family history / genetic status) have a strong genetic basis; epidemiological studies also show that most T2DM cases can be cured (Zheng et al., 2018). It suggests that it is caused by possible risk factors obesity that is defined as an individual who having 30 kg/m2 of body mass or higher. Excess adipose tissue

Received 30 July 2024; Accepted 15 August 2024

is almost dangerous step to diabetic individuals. Increases fat amount with insulin resistant cells is directly related, especially if the fat is concentrated in the abdomen (Gastaldelli, 2011). Inadequate exercise considers as the greater risk factor, among other benefits, as it helps control weight and lower blood sugar levels. In addition, a sedentary lifestyle may increase the risk of T2DM (Colberg et al., 2016). Worldwide, about 90% of patients develop T2DM, which is mainly associated with overweight. Obstructive sleep apnea and sleep disorders are common in obese adults. These are common risk factors for insulin resistance and glucose sensitivity, which together promote obesity and T2DM (DeFronzo et al., 2015; Wondmkun, 2020). Overweight can increase adipose tissue by increasing the secretion of adipokines and resistins, which contributing to T2DM (Wondmkun, 2020). Lack of exercise is a modifiable risk factor because exercise has benefits such as weight control, lowering blood sugar, and many others. In addition, a sedentary lifestyle can increase your risk of T2DM (Magkos et al., 2020).

Management of T2DM

Achieving good metabolic control and long-term maintenance of diabetes requires a combination of lifestyle changes and medications are necessary to achieving near-normal hemoglobin glycosides significantly and risk of macrovascular and microvascular problems will decrease (Musa and Dele, 2020).

Non-pharmacological therapy

Because many patients with T2DM are obese and often suffer from other metabolic disorders associated with insulin resistance syndrome, the main goals of diet and lifestyle changes are weight loss, glycemic control improvement and reduction the risk of coronary heart disease (CHD). Regular physical activities are of great importance for prevention as well as management of T2DM. Diet and physical activity are important elements of energy balance and are considered the basis of diabetes management, and adequate rest is essential to maintain energy and normal health. It is recommended that all people with diabetes get at least 7 hours of sleep per night (Wang et al., 2020; Igwesi-Chidobe et al., 2022; Nguyen et al., 2024).

Pharmacological therapy of T2DM

Patients with T2DM are guided for changing the type of diets, exercises program and gradually shift from monotherapies, dual therapies, or polypharmacy to insulin as the disease progresses. Many types of medications are recommended for the treatment of T2DM. The main drugs commonly used to treat hyperglycemia are sulfonylureas (increasing insulin production in the pancreatic islets), biguanide (decreasing glucose production in the liver), Gamma agonists of peroxisome proliferator-activated receptors (PPAR gamma) (increases insulin) and alpha-glucosidase inhibitors for intestinal glucose absorption, either alone or in combination with other hypoglycemic agents. Diet, lifestyle changes, and increased physical activity with metformin are usually at the forefront of treatment (Rani et al., 2020; Blahova et al., 2021). Metformin suppresses hepatic glycogen synthesis, insulin resistance in adjacent tissues, and increased GLP-1 production. After a meal (increasing insulin secretion), delay the meal. If the previous regimen is ineffective in promoting normoglycemia, sulfonylurea

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and meglitinide are usually the next drugs to be tried. Treatment with multiple subcutaneous insulin injections daily is effective in lowering blood sugar levels, and many patients often require insulin therapy if other treatments fail (Timmons and Boyle, 2022; Sheneman et al., 2024). Approximately 50% of patients require insulin therapy within 10 years of being diagnosed with T2DM.

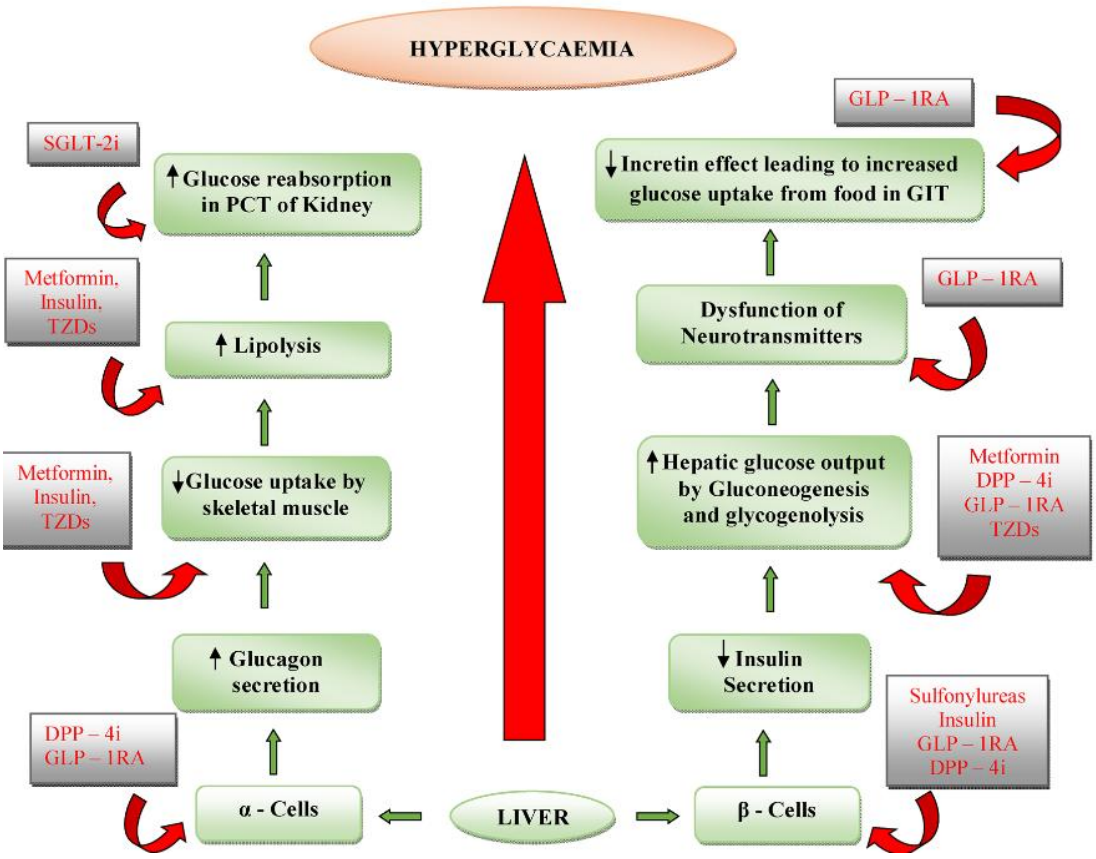

Figure (2): Medication goals for T2DM patients

Complications of T2DM

Diabetes is a disease that causes long-terms of macrovascular complication with development of peripheral vascular diseases, cerebrovascular diseases, and ischemic heart diseases which generally cause a death. At a microvascular level, DM causes visual impairments (retinopathies), renal diseases (nephropathies), as well as nerve cell damages (neuropathies), which most commonly cause chronic kidney diseases and irreversible blindness (Viigimaa et al., 2020). Diabetic retinopathy is one of the most common microvascular complications, followed by diabetic nephropathy and neuropathy (Goldney et al., 2023). All macrovascular problems gradually thin the vessel wall, affecting peripheral, carotid and coronary arteries, elevating the dangerous of heart infarctions, strokes, heart failure, and DM-related atherosclerosis caused by illness. It is also a serious complication of diabetes caused by the neuropathic parts of the lower extremities' micro vessels and macro vessels with peripheral arterial disease (Muzurović and Mikhailidis, 2021).

Microvascular Complications

A. Diabetic Nephropathy (DN)

Received 30 July 2024; Accepted 15 August 2024

It is an almost etiology of kidney diseases in developing countries. Elevated albumin has long been considered a marker for DN (Thipsawat, 2021).

B. Diabetic Retinopathy (DR)

It is a condition in which diabetic complications damage the retina, causing permanent eye damage and sometimes loss of vision. If left untreated, this problem can lead to blindness in the patient (Teo et al., 2021). Chronic hyperglycemia promotes the developing DR through increasing the vascular permeability that causes retinal ischemia. DR accounts for 5% of cases of blindness. The visual impairment caused by DR can reduce life quality of DM individuals with increases the treatment cost, which puts a heavy burden on the national health system. Earlier detection and actual managing of DR could be more active in prevention of acute loss of vision and blindness (Kropp et al., 2023).

C. Diabetic Neuropathy

It is considered a nerve damaging due to DM. This is the main chronic problem that affects (30-50%) of diabetics after failing to find other causes. It can affect the peripheral, autonomic and central nervous systems. About 80% of people with distal symmetric sensory neuropathy also experience chronic pain, insufficient restful sleep (Anandhanarayanan et al., 2022; Aktas, 2024).

Macrovascular Complications

By 2030, DM has expected as the seventh cause of death globally. Diabetic complications are primarily associated with peripheral vascular diseases as well as coronary artery disease and heart diseases, with more than half of diabetics causing high morbidity and mortality (Viigimaa et al., 2020). Atherosclerosis secondary to DM causes cerebrovascular disease, which causes death in DM patients with significantly reduces their quality of life. The combination of hyperglycemia and other risk factors like prolonged IR, obesity, hypertension, as well as dyslipidemia could play great roles for advancing of atherosclerosis (Maida et al., 2022; Feingold and Grunfeld, 2023). Peripheral artery disease represents a progressive disease manifested with stenosis and occlusion of medium and large, medium size arteries other than that supply heart or brain (Stone, 2022). It can affect lowered extremities rather than upper extremities vessel. It can cause repetitive fatigue, cramping sensation, or pain called intermittent claudication (Zaib et al., 2021).

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