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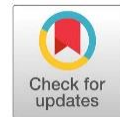
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Chronic Limb Ischemia: Awareness and Treatment in Primary Care

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Abstract

Chronic limb ischemia (CLI) is a type of peripheral arterial disease (PAD) that is still underdiagnosed and undertreated despite the increasing incidence, thus becoming a global health burden. The prevalence of PAD is quite high, approximately around 200 million globally in the adult population and increased drastically in older age population. It might be difficult to diagnose at an early stage because around 20-50% patients may be asymptomatic. More than 70% of primary physicians also did not notice that the diagnosis was already established during screening of the PAD patients. All these problems could increase the incidence of PAD in the following year. The untreated conditions will develop into a more severe form of PAD known as chronic limb-threatening ischemia (or critical limb ischemia), and patients are at a higher risk of having limb loss, and also increased morbidity and mortality. The primary physicians in the primary health facilities hold an important role in the early diagnosis and management of patients with CLI symptoms or with risk factors of CLI. Due to the limitation of diagnostic testing modality at primary health facilities, the physician can assess the ankle-brachial index (ABI) to determine the presence of CLI. Management of the disease is different for every patient and is customized based on the other comorbidities. Risk factors should be controlled in order to achieve a better outcome. A good management strategy will improve the condition. This review aims to describe how to give an early diagnosis and management for CLI patients in primary health care.

Keywords: Ankle-brachial index, chronic limb ischemia, exercise program, pharmacological therapy, risk factor

Abstrak

Chronic limb ischemia (CLI) merupakan salah satu jenis peripheral arterial disease (PAD) yang masih kurang terdiagnosis dan kurang tertangani meskipun insidensinya terus meningkat, sehingga menjadi beban kesehatan global. Prevalensi PAD cukup tinggi, sekitar 200 juta secara global pada populasi dewasa dan meningkat drastis pada populasi usia lanjut. Mungkin sulit untuk mendiagnosis pada tahap awal karena sekitar 20-50% pasien mungkin tidak bergejala. Lebih dari 70% dokter primer juga tidak menyadari bahwa diagnosis telah ditegakkan selama skrining pasien PAD. Semua masalah ini dapat meningkatkan insidensi PAD pada tahun berikutnya. Kondisi yang tidak diobati akan berkembang menjadi bentuk PAD yang lebih parah yang dikenal sebagai chronic limb-threatening ischemia (atau critical limb ischemia), dan pasien berisiko lebih tinggi mengalami kehilangan anggota tubuh, dan juga peningkatan morbiditas dan mortalitas. Dokter primer di fasilitas kesehatan primer memegang peran penting dalam diagnosis dini dan penanganan pasien dengan gejala CLI atau dengan faktor risiko CLI. Karena keterbatasan modalitas pengujian diagnostik di fasilitas kesehatan primer, dokter dapat menilai indeks pergelangan kaki-lengan (ABI) untuk menentukan keberadaan CLI. Penatalaksanaan penyakit ini berbeda untuk setiap pasien dan disesuaikan berdasarkan komorbiditas lainnya. Faktor risiko harus dikendalikan untuk mencapai hasil yang lebih baik. Strategi penatalaksanaan yang baik akan memperbaiki kondisi. Tinjauan ini bertujuan untuk menjelaskan cara memberikan diagnosis dini dan penatalaksanaan untuk pasien CLI di layanan kesehatan primer.

Kata kunci: Indeks pergelangan kaki-lengan, iskemia tungkai kronis, program latihan, terapi farmakologis, faktor risiko

INTRODUCTION

Peripheral arterial disease (PAD) is becoming a burden for the health system globally. PAD is closely related to atherosclerotic disease. The disease has affected more than 200 million people around the world and cause 12-15% mortality in Europe.^(1,2) In the United States, the disease affected 1.3% of the men population and 1.7% of the women population (ages 40-49 years). The prevalence was significantly increased in the older population with 29.5% of the men population and 24.7% of the women population who were more than 80 years.⁽³⁾ Chronic limb ischemia (CLI) is a type of PAD that is underdiagnosed and undertreated because the patient may be asymptomatic at the beginning. About 20-50% of the patients are asymptomatic.^(4,5) The burden is even higher due to unawareness of the physicians ($\geq 70\%$) that the diagnosis had already been established during PAD screening.⁽⁶⁾

However, during the progression of the disease, CLI would manifest in several symptoms and are related to the impairment of the quality of life. CLI is mainly associated with the presence of diabetes mellitus, dyslipidemia, hypertension, smoking, and also older age. These risk factors would damage the arterial system, reducing the blood flow causing poor perfusion to the tissue.⁽⁷⁾ Although the patient may experience mild symptoms, the prevention of further progression is crucial. The well-known severe form of CLI is critical limb ischemia. This manifestation could put someone at a higher risk of limb loss and cardiovascular disease.⁽⁸⁾ Critical limb ischemia affects 12% of the adult population and related to a quite high mortality rate, 25% at 1 year, and 60% at 5 years. The prognosis may become poorer for patients with critical limb ischemia, thus need a rapid diagnosis establishment and early management.⁽⁹⁾ It is also more common with the older age population.⁽¹⁰⁾

Diagnostic modality and management strategies in the hospital are able to treat the patient thoroughly.⁽⁴⁾ However, patients may come to the primary health facilities at the beginning to treat the symptoms. Limited modalities in the primary health facilities make the physician should be able to perform the simple yet reliable examination that is needed to establish the diagnosis of CLI. Thereby, the early management can be administered and would prevent complications. This study aims to understand and describe the role of primary health care for the diagnosis and management of patients with CLI.

DEFINITION OF CLI

CLI is often also defined as critical limb ischemia, thus both share a common definition. American Heart Association/American College of Cardiology (AHA/ACC) Guideline defines this disease as a condition which has some characteristics such as ischemic pain at rest, non-healed ulcers, and the presence of gangrene with the onset of ≥ 14 days. These characteristics may present in 1 or both legs with a presence of arterial occlusive disease objectively proven.⁽¹¹⁾ These symptoms are a result of poor peripheral perfusion caused by the chronic pathological process in the arterial system. Critical limb ischemia is also defined as a chronic limb-threatening ischemia (CLTI) by another guideline.⁽¹²⁾ It affected 11.08% of the PAD population annually.⁽¹³⁾

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF CHRONIC LIMB ISCHEMIA

The presence of CLI is highly associated with atherosclerotic process which is related to several risk factors such as smoking, diabetes mellitus, dyslipidemia, and hypertension. A study by Joosten et al. showed that smoking is one of the leading risk factor for CLI, affecting 44% of the population.⁽¹⁴⁾ An active smoker has a 4.3 times higher risk for developing symptomatic PAD (including CLI) and a former smoker has 2.3 times higher risk.⁽¹⁵⁾ While it is clear that an active smoker has an increased risk of developing PAD, the study on the passive smoker is lacking. However, two studies showed a similar association between passive smoking and PAD. The first study showed that 2.4% (134 of 5686) of the population who never smokes, had PAD.⁽¹⁶⁾ The second study showed that 3.2% of the population had intermittent claudication.⁽¹⁷⁾ Diabetes mellitus increases the risk of

PAD. Increased HbA1c level in diabetic patient also accounts for 26% risk for PAD. ⁽²⁾ Diabetic patients with PAD are also in risk of amputation, 5-times higher. ⁽¹⁸⁾ Infection rate is higher in the diabetic patients and this can increase the possibility of amputation in the patients. ⁽¹⁹⁾

Hypertension is an important risk factor after smoking and diabetes. Itoga et al. found that a systolic blood pressure ≥ 160 mmHg was related to a 21% higher risk of PAD. However, this study also found a relation between lower systolic blood pressure (< 120 mmHg) with PAD. ⁽²⁰⁾ The result of this study is different from other cohort studies who stated an association between a higher and not a lower systolic blood pressure with the risk of PAD. ^(21,22) The difference might come from the fact that Itoga et al. conducted a study on the population that had hypertension and other cardiovascular risk factor, while the other two studies were conducted in healthy population.

Dyslipidemia is associated with the progression of PAD and its complication. The increased ratio between total cholesterol and high-density lipoprotein cholesterol (HDL-C), triglyceride-rich lipoprotein, and also a decreased HDL levels are associated with incidence of PAD. ⁽²³⁾

DIAGNOSIS CONFIRMATION OF CHRONIC LIMB ISCHEMIA IN PRIMARY CARE

Chronic limb ischemia is diagnosed based on the clinical condition, supported by some supporting investigation. While some cases might need advanced imaging modality, the initial examination is important and can be done by the primary physician at the primary health care.

History taking

The primary physician must address the related signs and symptoms and also risk factors. The patient may have a symptom of claudication, pain at rest, walking impairment, and even an ulcer. Claudication is defined as a pain that happens while activity or exercise and resolve after 10 minutes of rest. It usually includes pain in the hip, buttock, calves, thigh, and feet. ⁽²⁴⁾ The ischemic rest pain is usually felt in the forefoot and metatarsal area. ⁽⁴⁾

Physical examination

In the CLI suspected patient, assessment of the arterial of the limb is very important. Physicians must palpate and address any abnormal pulses of the arteries (femoral, popliteal, dorsalis pedis, and posterior tibialis). ⁽²⁵⁾ The absence of dorsalis pedis pulsation might happen in 12% of patients, but the absence of posterior tibial pulse is always abnormal. Other physical findings such as audible bruits, nonhealing wounds or ulcers, gangrenous tissue, pallor at elevation, delayed capillary refill, and cool limbs. ^(9,26) Besides the examination of the affected limb, we must also examine the blood pressure on both arms to evaluate if there is a subclavian artery disease. 20 mmHg difference between both arms suggestive for the subclavian disease. ^(26,27)

Diagnostic testing

Suspicion of CLI must be supported with the presence of occlusive disease. However, there is limitation in the primary health care to perform a more advanced examination such as treadmill test, duplex ultrasound, computed tomography/magnetic resonance angiography (CTA/MRA). Resting ankle-brachial index (ABI) is an initial diagnostic test that can be done to confirm CLI in primary health facilities. ABI is a ratio of the highest systolic blood pressure of the foot (dorsalis pedis or posterior tibialis) divided by the highest systolic pressure of the arm. ⁽²⁸⁾ The interpretation of resting ABI is defined as abnormal (≤ 0.90), borderline (0.91-0.99), normal (1.00-1.40), and non-compressible (> 1.40). ^(29,30) ABI score of ≤ 0.90 shows reduced peripheral blood flow and is suggestive for the diagnosis with 95% sensitivity and 99% specificity. ABI < 0.4 is indicative of severe ischemia. Lower ABI shows the more severe ischemia. ⁽³¹⁾ However, an ABI more than 1.40 may be associated with peripheral calcification, a risk of having cardiovascular events, and impairment of quality of life. ^(32,33) It is recommended to measure ABI in patients with history and

physical examination suggestive for CLI and in patients with an increased risk for CLI without features on history and physical examination.

MANAGEMENT STRATEGY OF CHRONIC LIMB ISCHEMIA

Once the diagnosis of CLI is established, the management strategy should be initiated to prevent complications, reduce the risk of cardiovascular events, and improve the functional capacity. The early management strategy in primary health care includes pharmacological therapy and lifestyle modification.

Pharmacological therapy

The treatment using pharmacological agents in patients with CLI is customized, based on the comorbidities (hypertension, dyslipidemia, diabetes mellitus). Antiplatelet therapy using aspirin (75-325 mg/day) or clopidogrel (75 mg/day) can be given in symptomatic patients. (Class: I, Level of evidence: A). Antiplatelet therapy is indicated as secondary prevention in patients with high-risk of cardiovascular events.⁽¹¹⁾ In PAD patients who are asymptomatic, the use of aspirin may reduce the risk of cardiovascular events despite the study conducted by Flowkes et al. showed no benefit of aspirin in asymptomatic PAD patients.^(11,34) The use of clopidogrel is highlighted in a study by Katsanos et al. In this study, clopidogrel was able to reduce the risk of major adverse cardiovascular events (MACE). Clopidogrel can be used as a single therapy for PAD patient to prevent the bleeding risk if combined with aspirin.⁽³⁵⁾

Other comorbidities must be treated according to the guidelines. Statin therapy is indicated in all patients with PAD (asymptomatic and symptomatic) and it is associated with reduced cardiovascular events and mortality. This is supported by the data from the Reduction of Atherothrombosis for Continued Health (REACH) registry which showed a 17% reduction of the adverse CV events. In CLI patients, the low-density lipoprotein cholesterol (LDL-C) should be maintained at < 70mg/dl or $\geq 50\%$ from the initial LDL-C levels (if baseline: 70-135 mg/dl).⁽³⁶⁻³⁸⁾ For hypertensive condition, administration of angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) are also associated with a decreased cardiovascular events with the goal to maintain the blood pressure at < 140/90 mmHg.⁽³⁷⁾ In diabetic patients, the HbA1C levels should be maintained at < 7% to prevent further complication.⁽³⁹⁾

Symptomatic treatment for pain is also important to improve the quality of life. Physician could prescribe paracetamol or non-steroidal anti-inflammatory drugs (NSAID) to eliminate the pain, although those medications might not be sufficient.^(33,40) However, we have to be aware giving the NSAID because it can disrupt the healing process of the wound.^(41,42)

Lifestyle Modification

Smoking has been a major risk factor in CLI development. Smoking cessation must be advised to the patient. A study by Hennrikus et al. showed that an intensive smoking cessation program was associated with 21.3% of smoking abstinence at a 6-month follow-up.⁽⁴³⁾ By stopping on smoking, it will lower the mortality of the patient and also will increase the survival with amputation-free.⁽⁴⁴⁾ Some additional therapy could be given to help the smoking cessation program, such as varenicline, bupropion, and nicotine replacement therapy.⁽¹¹⁾

Physical activity is important for CLI patients because it reduces the risk factors' role in the progression of the disease. It is recommended for patients to do structured exercise therapy. It is also able to reduce the claudication symptom. Several studies was able to show the beneficial effect of exercise (18 months – 7 years) in claudication.^(45,46) Structured exercise therapy (SET) can be done in a health facility or at home. SET program at the health facility (Class: I, Level of evidence: A) includes an intermittent walking exercise which is supervised by the healthcare provider. The exercise is performed with a minimum duration of 30-45 minutes/session, with 3 sessions/ week for a minimum of 12 weeks. The patient can do the self-directed SET program at home or community-

based (Class: IIa, level of evidence: A) with the guidance and exercise regimen prescription from the healthcare provider. ⁽¹¹⁾ Patients who do not have improvements after therapy and even experience limb-threatening condition should be referred to the advanced health facilities to undergo revascularization therapy and wound management by the wound specialist team. ⁽⁴⁷⁻⁴⁹⁾

Patients with chronic limb-threatening ischemia (CLTI) need a more adequate approach with a multi-specialists team. The goals are: to control the symptoms, increase the quality of life, and prevent any complications (medical goals); revascularization to preserve the limb (interventional goal); and proper monitoring after treatment (surveillance goal). Primary care physicians have an important role and should be able to give care to achieve the medical goals. ⁵⁰

PREVENTIVE STRATEGY

Reducing the risk of CLI progression is the goal especially in the vulnerable population. Physical activity can prevent the development of the disease. It is related to its effect on controlling the atherosclerotic factor in the patient. The benefit of physical activity is also related to its function on increasing nitric oxide, thus preventing endothelial dysfunction. ⁵¹ Other preventive strategies include the maintenance or control of lipid level, blood pressure, and also blood glucose level. ⁵²

CONCLUSION

CLI is becoming a burden for the health system and primary health care has become an essential part as the first line for the diagnosis and management of patients with CLI. Resting ABI is a reliable diagnostic testing for patients with CLI suspicion. $ABI \leq 0.90$ is suggestive of the presence of ischemia. Early management is needed to prevent further complications. Management includes pharmacological therapy and lifestyle modification to reduce cardiovascular risks.

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