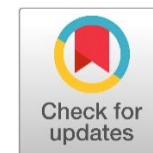




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Review Article:

The Effect of Cilnidipine on Insulin Sensitivity

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Article Information

Article history:

Received on: 11 September 2023

Revised on: 23 October 2023

Accepted on: 28 October 2023

Published on: 30 December 2023

Keywords:

Cilnidipine,
Insulin sensitivity,
Diabetes

Abstract

Background: Cilnidipine, a common hypertension medication, is now being studied for its potential to improve insulin sensitivity, which plays a key role in regulating blood sugar levels. Recent research suggests that cilnidipine may benefit individuals with both hypertension and insulin resistance, offering a promising avenue for further investigation and potential therapeutic applications. **Objective:** The present study aimed to investigate the influence of cilnidipine on insulin sensitivity, seeking to comprehend how this medication affects the body's capacity to utilize insulin efficiently. **Methods:** The current literature search was conducted using diverse databases, primarily including PubMed, Elsevier, Google Scholar, and the Iraqi Virtual Science Library. The search was limited to publications up to [2009 - 2023], and the keywords "Cilnidipine" and "Insulin Sensitivity" were used to identify relevant articles. Inclusion and exclusion criteria were applied to filter the search results, and the number of papers retrieved meeting these criteria was recorded for further analysis. **Results:** indicate that cilnidipine may have a positive impact on insulin sensitivity in individuals with hypertension and type 2 diabetes. This suggests that cilnidipine could potentially be a beneficial therapeutic option for addressing insulin resistance in these patients. However, it is crucial to note that further research is necessary to confirm these findings and evaluate the long-term effects of cilnidipine on insulin sensitivity. **Conclusion:** The results of this study indicate a potential positive impact of cilnidipine on insulin sensitivity in individuals with both hypertension and type 2 diabetes. This suggests that cilnidipine could serve as a promising therapeutic option for addressing insulin resistance in these patients.

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1. Introduction

One of the most prevalent metabolic abnormalities that contribute to hyperglycemia in people with obesity, type two diabetes ("also known as non-insulin-dependent diabetes mellitus, or NIDDM"), or both is insulin resistance (1). Recently, it was shown that individuals with essential hypertension frequently have hyperinsulinemia and/or glucose intolerance (2). In addition, individuals with essential hypertension also have resistance to insulin-stimulated glucose absorption, as shown by the glycemic hyperinsulinemia clamp method (3).

It has been demonstrated that certain commonly used antihypertensive drugs change atherogenic risk profiles and insulin sensitivity. Beta-adrenoceptor blockers and thiazides

reduce the sensitivity of insulin and exacerbate dyslipidemia. Alpha1-blockers, ACE inhibitors, and other medications that block the ACE decrease arterial lipid profiles and heighten insulin resistance (4). Insulin sensitivity is decreased by the shorter-acting dihydropyridine calcium channel antagonist nifedipine. Due to their growing vasodilatory action, long-lasting calcium-channel antagonists like amlodipine and barnidipine have been shown to increase insulin sensitivity. Some medications might not accelerate the sympathetic nervous system as strongly as nifedipine does. The impact of cilnidipine, which blocks N-type Ca channels, on lipid and glucose metabolism as well as renal function make it more beneficial for those with hypertension and diabetes mellitus (5).

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How to cite:

Mahmood, A., M., Mohammad, Sh., H., (2023). The Effect of Cilnidipine on Insulin Sensitivity. *Iraqi J. Pharm.* 20(Supp-01), 210-216.

DOI: <https://doi.org/10.33899/iphr.2023.143299.1060>

Cilnidipine's multifaceted effects on lipid and glucose metabolism, coupled with its influence on renal function, have raised intriguing possibilities for individuals grappling with both hypertension and diabetes mellitus. These conditions are becoming increasingly prevalent in Japan and worldwide, underscoring the urgent need for effective management strategies. The potential of cilnidipine as a valuable therapeutic option is illuminated by this review, offering hope for improved outcomes and enhanced quality of

1.1 The Relationship Between Sympathetic Nerve Activity and Various Calcium Channel Subtypes

At least six kinds of calcium channels may be distinguished, depending on pharmacological and electrophysiological data: L-, N-, P-, Q-, R-, and T-type (7). T- category calcium channels are slow-to-activating but fast-to-deactivate low-voltage-activated (LVA) calcium channels. All five of the remaining calcium channel types are high-voltage-activator (HVA) calcium channels, where depolarization occurs at a voltage of roughly 40 mV. Inside excitatory cells, including neurons, heart muscle cells, and smooth muscle, HVA calcium channels control several biological activities such as muscle contraction, neuronal electrical activity, and neurotransmitter and hormone release. Calcium channels are composed of 1, 2, and 3 subunits, as demonstrated by molecular biology methods employing skeletal muscle L-type calcium channels. The most important function is performed by the calcium transmission channel, The L subunit specifically produces a compound, and there have been twelve 1 subunits cloned as well have also been cloned, and based on how similar their

life for individuals grappling with the complex interplay of hypertension and diabetes. By understanding the higher risk of proteinuria in those with both conditions and the heightened incidence of hypertension in individuals with diabetes, a deeper appreciation of the interconnected challenges faced by these patients can be achieved by healthcare providers and researchers, ultimately leading to more tailored and effective approaches to their care. Passive voice has been used in this revised version of your text (6). gene sequences are, they have been grouped into 3 subdivisions called Cav1.x, Cav2.x, and Cav3.x (8).

1.2 Relationship between Sympathetic Nerve Activity and Hypertension

High blood pressure is just one of several signs of underlying physiological issues in the complex and difficult illness known as hypertension. Unique of the key factors contributing to the development of hypertension is sympathetic nerve achievement. According to Julius, borderline hypertensive individuals experience hyperkinetic conditions five times more frequently than the general population and normotensive patients do. Heart rate and cardiac output are both increased in a hyperkinetic condition. In an investigation of individuals with borderline hypertension using microneurography, it was found that borderline hypertensive patients' muscular sympathetic nerve activity was much greater than that of normotensive people⁹ as shown in **Figure 1**. On the other hand, in patients with chronic renal failure, the central-acting antihypertensive moxonidine treatment lowers muscular sympathetic nerve activity, as shown in **Figure 2** (8).

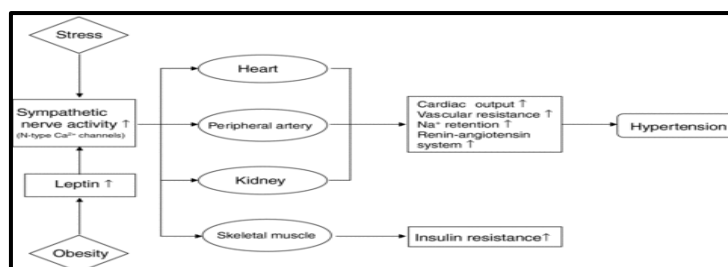


Figure 1. Diagram of relative of N-type Ca^{2+} means to hypertension (8)

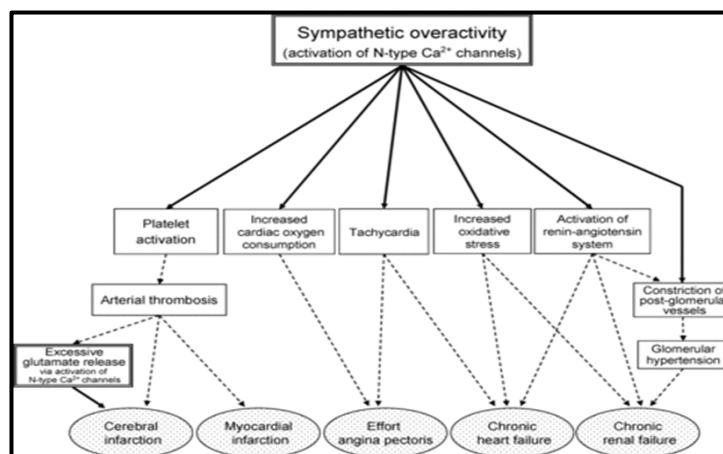


Figure 2. Diagram of relation of N-type Ca^{2+} channels to major complications of hypertension (9)

1.3 Fourth Generation Ca^{2+} Channel Blocker: Cilnidipine and Role in Various Clinical Setting

Cilnidipine, inhibits both N-type and L-type calcium channels, as seen in **Figure 3**. A halothane-anesthetized canine model was utilized to examine the extent of cilnidipine's anti-sympathetic effects. A dosage of cilnidipine that dropped the average B.P by 14 mmHg revealed a 37%

reduction of sympathetic tachycardia brought on through the vasodilator acetylcholine (10). More than 90% of the sympathetic tachycardia caused by vasodilators has been shown to be suppressed by propranolol. Because of this, the pharmacological profile of the antihypertensive medication cilnidipine may be like the results of combining an isolated L-type calcium channel blocker with a slight amount of a β -adrenergic receptor blocker (11,12).

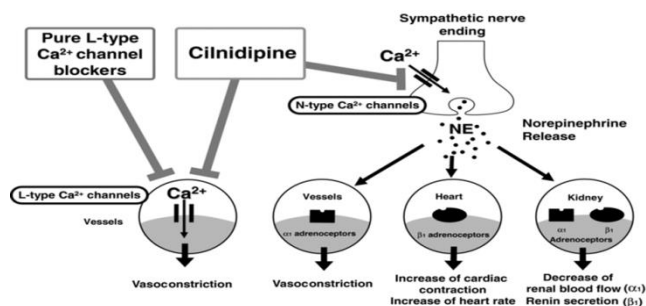


Figure 3. Diagram of the L/N-dual action of cilnidipine (12)

1.3.1 Impact of Cilnidipine on Metabolic Syndrome

As elements of the metabolic syndrome, central obesity is associated with hypertension, resistance to insulin, and dyslipidemia, and a rise in body weight is associated with sympathetic activation. According to several studies, obesity is associated with elevated plasma norepinephrine levels and muscle sympathetic nerve activity (13). Furthermore, one of the factors supporting the long-term progression of hypertension may be central obesity. "Due to this, it becomes evident that effectively managing sympathetic activity is essential when treating metabolic syndrome (14). The Islets of Langerhans cells produce glucagon and pancreatic insulin, which are started by the influx of calcium through N-type calcium channels (15). Glucose tolerance increased without altering insulin sensitivity in research utilizing N-type calcium channel 1B-deficient homozygous knockout mice fed a regular diet; however, body mass was reduced in animals administered a diet high in fat (16). Another research found that although insulin resistance decreased following cilnidipine treatment, insulin sensitivity was much worse in fructose-fed rats than in controls (17). This shows that N-type calcium channels are crucial for the control of glucose. In hypertensive individuals with type 2 diabetes, cilnidipine was found to significantly reduce the catecholamine levels in the 24-hour urine, potentially reducing resistance of insulin. The homeostasis equilibrium model assessment HOMA-R, or homeostatic model assessment of insulin resistance, is a simple calculation that can be used to estimate insulin resistance, also found that cilnidipine medication decreased fast blood immunoreactive insulin (F-IRI) and the insulin resistance index, despite increasing blood DHEA. Dehydroepiandrosterone is a hormone produced by the adrenal glands, and DHEA-sulfate (DHEA-S) (5).

1.3.2 Cilnidipine's Vasodilatory Effect and Its Potential Impact on Insulin Sensitivity

One possible explanation is that cilnidipine may improve insulin sensitivity by reducing the activity of other hormones that promote insulin resistance, such as angiotensin II and aldosterone (18). Another possible explanation is that cilnidipine may improve insulin sensitivity by increasing the production of nitric oxide, a vasodilatory and anti-inflammatory molecule (19).

1.3.3 Antihypertensive Effects

Hypertension demonstrated that daily administration of cilnidipine at doses ranging from 5 mg to 20 mg for a duration of one to three weeks led to a significant reduction in 24-hour average blood pressure. Specifically, these studies observed a decrease from an average of 149.4/88.2 mmHg to 141.3/82.2 mmHg, with no concurrent changes in heart rate. As a result, cilnidipine is a potent antihypertensive drug that seldom results in tachycardia or excessively low blood pressure. Cilnidipine, an Effective Antihypertensive Medication, Demonstrates Minimal Impact on Blood Pressure and Heart Rate (19). Its vasodilatory properties, initially identified in both in vitro and in vivo studies, are consistently validated in clinical settings. This revised sentence maintains the key information while improving the flow and clarity of the statement. Twenty-four clinical studies on hypertensive and severely hypertensive patients have demonstrated the antihypertensive effects of cilnidipine. Treatment with cilnidipine and angiotensin receptor blockers in a trial of 2920 hypertensive individuals significantly lowered the heart rate, especially in those with higher basal rates, with few side effects related to central neurological function (20).

1.3.4 Other Effect on Heart

Impacts patients with hypertensive heart disease who were using cilnidipine for six months saw an improvement in L-ventricle diastolic function (LV) (21). Taking cilnidipine 5–10 mg/day for 8 weeks can recover left ventricular systolic performing without growing blood pressure, according to the CANDLE study and other clinical investigations (21-23). Cilnidipine lowers left ventricular mass (LVM) in essential hypertension more than quinapril. In a rabbit model of myocardial infarction, the cardioprotective effects of cilnidipine were examined (24). During the ischemia and reperfusion phases, cilnidipine decreased myocardial interstitial norepinephrine levels, which decreased the size of the myocardial infarct and the incidence of ventricular premature beats. Additionally, in vivo research shows that cilnidipine reduces anomalies in ventricular repolarization in the canine model of long QT syndrome and has antianginal properties in the laboratory model of vasopressin-induced angina (25).

1.3.6 Effect on Kidney

Elevated blood pressure stands as a foremost contributor to the advancement of kidney disease. Furthermore, chronic renal failure, elevated urea protein levels, and albuminuria individually pose significant risks for cardiovascular and cerebrovascular diseases (26). The CARTER medicinal studies establish that cilnidipine offers improved renal defense compared to other dihydropyridine Calcium Channel Blockers (CCBs). In 339 individuals with hypertension and renal disease, the 42-CARTER study, a randomized trial conducted across multiple centers with an open-label approach, provides valuable insights into the subject matter, investigated the antiproteinuric effects of cilnidipine with amlodipine as Figure 4 (27). Cilnidipine appears to be greater than amlodipine in slowing the development of proteinuria in hypertensive individuals whilst paired through a renin-angiotensin system inhibitor (23,28).

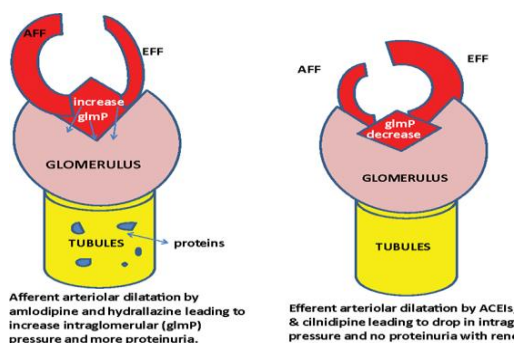


Figure 1. Impact of Cilnidipine on Kidney²¹

1.3.5 Influence on CCBs stimulated ankle edema

Podocytes serve as a vital permeability barrier within the glomeruli, effectively preventing the passage of substantial molecules such as albumin (29). The most typical symptom of a damaged glomerular filtration barrier is albuminuria. In a number of glomerular diseases that result in proteinuria, podocytes' structural integrity has been compromised. A reduction in the number of podocytes has been connected to the forty-three diabetic nephropathy (30,31). By promoting vasodilation in both the afferent and efferent arterioles within the glomeruli, cilnidipine protects the glomeruli (23). This lowers glomerular pressure, which significantly lowers proteinuria. An open label, randomized, controlled study including 60 patients with CKD was conducted to examine the effects of cilnidipine. After a year of cilnidipine therapy, proteinuria and heart rate significantly decreased; however, in patients receiving CCB therapy (L-CCB), proteinuria rose, and heart rate remained stable (33). The urine albumin/creatinine ratio was demonstrated to be considerably lower after 6 months of cilnidipine medication compared to amlodipine treatment in this study, which examined the antioxidant and antiproteinuric advantages of cilnidipine compared to amlodipine (34). New calcium channel subtype-blocking CCBs have been developed within the past ten years³⁵. Long-acting CCBs have been used to treat hypertension, but alternative CCBs have also been used, chosen depending on the characteristics of the calcium channel subtype they block (24,36). Amlodipine is well recognized for its ability to affect the L-type calcium

channels that are abundantly expressed in vascular smooth muscle. whereas cilnidipine also affects the copious N-type calcium channels found in the sympathetic nervous system (37,38). In order to compare the effectiveness of amlodipine and cilnidipine in patients with hypertension (39-42).

We employed a cross-over study (39) aimed to compare the clinical and biochemical profiles of patients with mild to moderate hypertension treated with Amlodipine and Cilnidipine. A total of 140 patients were divided into two groups: Amlodipine (Group-A) and Cilnidipine (Group-B), and both groups had been receiving their respective medications for over six months. The study found that both drugs were equally effective in reducing blood pressure, with Cilnidipine showing a slightly greater reduction. There was no significant change in heart rate between the two groups. Cilnidipine also resulted in a comparatively shorter QT/QTc interval compared to Amlodipine. Demographic parameters were well-matched between the groups, and there were no significant differences in biochemical parameters such as serum creatinine, albumin, globulin, total protein, serum Na⁺, fractional excretion of Na⁺, serum osmolality, and vanillyl mandelic acid. both Amlodipine and Cilnidipine are effective antihypertensive drugs. Cilnidipine may provide a slightly better reduction in blood pressure and a shorter QT/QTc interval without significant differences in other biochemical parameters compared to Amlodipine (39).

1.4 Drawback of Cilnidipine

Patients exhibiting pronounced aortic stenosis, suffering from cardiogenic shock, presenting a recent record of unstable angina or myocardial infarction (MI), or grappling with heart failure, or high blood pressure should not use cilnidipine⁴³. Adults should take 5–10 mg of cilnidipine orally once a day. The dose can be raised to 20 mg if required. In contrast to 5mg of amlodipine, 5mg of cilnidipine appears to be rather ineffective as a single antihypertensive medication. Sometimes starting with 10 mg of cilnidipine is essential for proper antihypertensive activity. However, we were unable to find sufficient clinical trial data to back up this assertion (18).

2. Conclusion

Cilnidipine may improve insulin sensitivity. Studies suggest that cilnidipine may enhance endothelial function, increase skeletal muscle glucose absorption, and improve lipid metabolism, but these findings are preliminary. Future studies should include larger sample sizes, longer-term follow-up, and rigorous methodologies to establish a conclusive link. Exploring the underlying mechanisms of cilnidipine's effects on glucose metabolism is also essential. Additionally, by exploring the underlying mechanisms of action of cilnidipine, these studies could lead to the development of new and more effective treatments for these conditions. To effectively treat patients with hypertension who also have insulin resistance and/or diabetes mellitus, it is crucial to take advantage of cilnidipine's beneficial effects on glucose metabolism. Cilnidipine may improve insulin sensitivity, potentially benefiting individuals with conditions like hypertension and diabetes mellitus. Forty-nine obese individuals with hypertension who received 10 mg of cilnidipine showed reduced insulin resistance.

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تأثير سيليني ديبين على حساسية الأنسولين

الخلاصة:

الهدف: أجريت الدراسة الحالية على تأثير سيليني ديبين على حساسية الأنسولين لفهم كيفية تأثير هذا الدواء على قدرة الجسم على استخدام الأنسولين بشكل فعال. **معلومات أساسية:** سيليني ديبين عبارة عن حاصرات لقنوات الكالسيوم تستخدم بشكل شائع لعلاج ارتفاع ضغط الدم. ومع ذلك، فقد أشارت الدراسات الحديثة إلى أن سيليني ديبين قد يؤثر أيضًا على حساسية الأنسولين. تشير حساسية الأنسولين إلى مدى استجابة خلايا الجسم للأنسولين، وهو هرمون ينظم مستويات السكر في الدم. عندما تكون الخلايا حساسة للأنسولين، فإنها تكون قادرة على امتصاص الجلوكوز بكفاءة من مجرى الدم واستخدامه للحصول على الطاقة. ومع ذلك، عندما تصبح الخلايا مقاومة للأنسولين، فإنها تكون أقل قدرة على الاستجابة للأنسولين، ويمكن أن ترتفع مستويات الجلوكوز في مجرى الدم. اقترحت العديد من الدراسات أن سيليني ديبين قد يحسن حساسية الأنسولين لدى مرضى ارتفاع ضغط الدم. على سبيل المثال، وجدت دراسة نشرت في *Journal of Clinical Hypertension* أن سيليني ديبين يحسن حساسية الأنسولين لدى مرضى السكري من النوع 2 وارتفاع ضغط الدم. وجدت دراسة أخرى نشرت في مجلة ارتفاع ضغط الدم أن سيليني ديبين يحسن حساسية الأنسولين لدى المرضى الذين يعانون من ارتفاع ضغط الدم الأساسي. **الطرق:** يتم تجنيد قواعد بيانات مختلفة للمواد المنشورة بشكل رئيسي من PubMed و Elsevier و Google Scholars والمكتبة الافتراضية للعلوم العراقية. **النتائج:** توضح هذه المراجعة وفقًا لدراسة نشرت في مجلة البحوث السريرية والتشخيصية في عام 2016، أن سيليني ديبين يعمل على تحسين حساسية الأنسولين لدى مرضى الضغط مرض السكري من النوع الثاني. وخلصت الدراسة إلى أن سيليني ديبين قد يكون خيارًا علاجيًا مفيدًا لتحسين مقاومة الأنسولين لدى هؤلاء المرضى. هناك حاجة إلى مزيد من البحث لتأكيد هذه النتائج وتحديد الآثار طويلة المدى لسيليني ديبين على حساسية الأنسولين. **الاستنتاج:** قد يكون سيليني ديبين خيارًا علاجيًا مفيدًا لتحسين حساسية الأنسولين لدى مرضى الضغط ومرض السكري من النوع الثاني.

الكلمات المفتاحية: سيليني ديبين، حساسية الأنسولين، السكري .