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Research Article

Assessment of the Effect of C-Peptide Level on Na-K ATPase Activity In Individuals with Type II Diabetic Peripheral Neuropathy

Eman H Al-Rikabi[1], Oda M Yasser[2], Mazin J Mousa[3]

[1,2]Department of Chemistry, College of Science, University of Babylon, Babylon Governorate, P.O. 51002, Iraq.
[3]College of Pharmacy, University of Babylon, Babylon, P.O. 51002, Iraq.
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I N F O

Corresponding Author:
Eman H Al-Rikabi, Department of Chemistry, College of Science, University of Babylon, Babylon Governorate, P.O. 51002, Iraq.
E-mail Id:
alrikabieman@gmail.com
Orcid Id:
https://orcid.org/0000-0003-0719-543X
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A B S T R A C T

Background: Both Type 1 and Type 2 diabetes can cause neuropathy, which is a frequent and severe consequence. C-peptide depletion may be partly related to in the occurrence of certain diabetic complications. It has been demonstrated that even a little amount of residual C-peptide has a considerable metabolic advantage.

Objective: The study's objective was to predict the relation of plasma C-peptide levels in patients with diabetic neuropathy, and its effect on Na-K ATPase activity.

Design and Methods: In this case-control study, 150 individuals have been included: 80 patients with diabetic neuropathy, 40 diabetics without neuropathy and 30 non-diabetic subjects as a control. Patients in the first group were carefully chosen based on their clinical symptoms and nerve conduction studies results. The assessment of plasma C-peptide was done by ELISA, Na-K ATPase enzyme activity by spectrophotometer, and HbA1C by HPLC.

Results: Mean plasma C-peptide level and Erythrocyte Na-K ATPase activity were substantially lower in neuropathy type 2 DM patients compared to diabetes without neuropathy and control (p= 0.002, 0.000 respectively). The negative correlation between C-peptide with HbA1c, and diabetes period were all negligible (p= 0.447,0.098), Even though there was a notable negative correlation with age (p= 0.03). On the other hand, the relationship linking C-peptide and Na-K ATPase enzyme activity was shown to be insignificant (p=0.69).

Conclusions: Diabetic neuropathy is related to a low C-peptide level. The association between C-peptide and Na-K ATPase enzyme activity, on the other hand, was shown to be insignificant. C-peptide HbA1c, and duration of diabetes all had minor negative associations.

Keywords: C-Peptide, Diabetic Neuropathy, HbA1C, Erythrocyte Na-K ATPase

Introduction

Diabetic neuropathy is a common chronic illness that is a common complication of both type 1 and type 2 diabetes,[1] including serious clinical implications such as pain, sensory deprivation, foot ulceration, and limb amputatio.[2] Neuropathy involves several different syndromes, the most common of which is diabetic polyneuropathy (DPN), which is distinguished by symmetric, mostly sensory polyneuropathy that is often combined with autonomic polyneuropathy.[3,4,5] Though hyperglycemia plays a part in the growth of diabetic neuropathy, tight blood sugar control doesn't really remove the chances of DPN in individuals with type 2 diabetes, suggesting that other problems must be addressed[6]. DPN has several underlying factors, namely inherited predispositions[7,8] and a slew of metabolic and molecular disorders resulting from high blood sugar, insulin, and C-peptide deficiency.[1,2,9-13] Otherwise, the impact of gender, age, stature, and cigarette smoke still debatable.[14]

C-peptide is a 31-amino acid linker chain cleaved from proinsulin by prohormone convertase enzymes in beta cells to produce the mature, functional insulin hormone.[15] C-peptide is used as a clinical indicator for pancreatic beta-cell activity since it is secreted in equimolar amounts of insulin and has a nearly five-fold longer half-life than insulin.[16-18] Despite its reputation as a simple, biologically inert compound, recent research has revealed that C-peptide is a biologically effective hormone with beneficial ability for the management of diabetes complications.[18] Much new research on C-peptide physiology has emerged in the last 20 years; see Wahren et al. for an overview.[19] C-peptide has been shown to bind directly to cell membranes,[20] and to induce intracellular signaling through G-protein– and Ca^{2+}dependent pathways,[21,22] resulting in increased expression of endothelial nitric oxide,[23] Na-K ATPase,[24] and many transcriptions of importance for antioxidative, anti-inflammatory, and cell-protective reactions.[25,26] In experimental diabetic animals and people with type 1 diabetes, C-peptide supplementation has been found to enhance peripheral and autonomic nerve function. While the interaction with C-peptide and type 2 diabetes efforts is unknown. Other findings exposed that residual insulin release, as measured by blood C-peptide amounts, protects diabetic neuropathy, although others found no such consequence[16] or came to the opposite conclusion.[27]

It is salient to stress that several researchers had reported a strong evidence of association of DPN, Na-K ATPase dysfunctions, and keratoconus (a corneal disorder).[28] A Na-K ATPase pump found in the peripheral membranes of endothelial cells maintains proper retinal hydration. As the corneas become oedematous, this pumping activity appears to break down in dysfunctional corneas,[29] probably via mechanisms of collagen crosslinking.[30] It was also found that many enzymes (like Na-K ATPase) cause a reduction in collagenous tissue stiffness; therefore, they may contribute in the progression of keratoconus.[31]

As a result, the aim of this research, was to find a connection between C-peptide levels and Diabetes duration, Age, HbA1C, Body Mass Index (BMI), and Erythrocyte Na/K ATPase activity in hospital-based Iraqi type 2 diabetic patients with neuropathy.

Methodology

Study Design

The study is a case-control, blood samples were collected from patients complaining of Type 2 DM registered in the Diabetes-care center in Merjan Teaching Hospital in Babylon Governorate, Iraq. The age range of the participating patients ranged from (30-70) years. These cases had divided into three groups, diabetic peripheral neuropathy (DPN) cases (80), diabetic patients without neuropathy (positive control group) (40), and healthy control group (negative control group) (30). All patient details had collected, including disease duration, degree of control of blood glucose, and the concomitant illnesses. The details of anti-diabetes and concomitant medications had collected. Patients with coexisting cardiac or renal disorders were excluded.

Ethics Issues

Ethical approval was obtained from the scientific committee of Merjan Teaching hospital and centre of diabetes in Babylon province. To gain the verbal acceptance from participating patients, the objectives of this study were explained to all participants in the current study.

Chemicals

All chemical substances were attained from standard commercial suppliers.

Collecting Blood Samples

Venous blood samples were collected in Na-EDTA tubes as an anticoagulant, immediately transferred to the lab, and centrifuged at 3000 X g. The plasma had separated into a different test tube and frozen for estimation of C-Peptide levels. Meanwhile, the lower cellular layer were immediately treated for the preparation of red cell membrane ghosts.

Methods

Plasma C-peptide levels were measured by Human C-peptide direct sandwich ELISA method Kit (CalBiotech). Glycated haemoglobin (HbA1C) was measured by HPLC. Erythrocyte Na-K ATPase activity was measured conferring to the methods described in our article published previously[32]. The BMI was determined by dividing the weight in kilograms by the square of the height in meters.

Statistical Analysis

SPSS software (IBM Corp., 2012) was used to complete all statistical computations. Armonk, NY: IBM Corp. The

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USA, IBM SPSS Statistics for Windows, Version 21.0) and Microsoft Excel (2010, Microsoft Corp. USA). All of the data was accessible as mean ± SE. A $p < 0.05$ was measured statistically significant. Analysis of variance (One Way Anova) Test was used to estimate the presence of significant differences. Regression investigation to assess the presence of correlations. Chi-square test to evaluate the categorically association variables, agreeing to (sole et al.,2006).[33]

Results

The current study involved 150 subjects which were separated into three categories: G1 type II diabetic patients with peripheral neuropathy (N: 80, 53.3%), G2 patients with type II diabetes without neuropathy (N: 40, 26.7%), and G3: healthy control subjects (N: 30, 20.0%). According to the Chi-square test (Table1), there is an intimate association comprising duration of diabetes and age in patients with diabetic neuropathy (p≤0.001, ≤0.001) respectively, although no such relation existed between BMI and neuropathy (p=0.810). Two-way ANOVA revealed a significance of C-peptide with all three groups with a P-value of 0.002, the amount of C-peptide in diabetic patients of neuropathy (1.170±0.10) differed significantly from diabetic patients lacking neuropathy (1.71±0.19) and control participants (1.96±0.28).

In the same context, erythrocyte Na-K ATPase activity revealed a considerable difference in patients with neuropathy compared to diabetic group, and healthy control group (381.94±18.00, 498.28*±22.98 and* 837.20±61.43 respectively) with a P≤0.001. There was a significant difference amongst experiment and control groups in age with means of 59.39±0.99, 53.93±1.52, and 30.80±0.98 respectively. Mean BMI: 27.91±0.68, 28.90±0.80, and 27.20±0.95 with no statistical significance (P=0.444). The level of HbA1C was statistically significant between groups (P≤0.001) with means of 9.42±0.25, 10.40±0.35, 5.23±0.05 respectively as shown in Table 2.

Table 3 shows the statistical correlation between C-peptide and enzyme activity of Na-K ATPase, there is an insignificant positive relationship (P= 0.694). Oppositely, the correlation between C-peptide with HbA1c, and duration of diabetes were insignificant negative (P = 0.447,0.09 respectively), but there is a significant negative correlation with age (P= 0.030), Also, there was no relationship between C-peptide level and BMI (P=0.997).

Table 1.Chi-Square Tests of BMI, Age and Diabetes Duration between Patients with Neuropathy and Control Groups

Parameter	Pearson Chi-Square	p-value
BMI	.058[a]	.810
Age	118.314[a]	0.000[b]
Duration of diabetes	68.571[a]	

0 cells (0.0%) have expected count less than 5. The minimum expected count is 11.45.

Based on 10000 sampled tables with starting seed 2000000.

Table 2.C-Peptide (ng/ml), HbA1C (%), Age of members, Erythrocyte Na-K ATPase activity (*µg* Pi\g protein), Endogenous digitalis (%), and Body Mass Index (BMI, Kg/m2) for diabetic neuropathy patients relative to diabetics without neuropathy and stable individuals

Parameters	Diabetic neuropathy (Mean ± SE)	Diabetes mellitus (Mean ± SE)	Control (Mean ± SE)	P value
C-peptide (ng/mL)	1.17 ± 0.10	1.71 ± 0.19	1.96 ± 0.28	0.002*
C-peptide			**Mean difference**	**p-value**
	Diabetic neuropathy	Diabetic without neuropathy	-0.541013*	0.016
	Diabetic neuropathy	Control	-0.794313*	0.001
Erythrocyte Na-K ATPase activity (µg Pi\g protein)	381.94 ± 18.00	498.28 ± 22.98	837.20 ± 61.43	0.001*
Enzyme activity of Na-K ATPase			**Mean difference**	**p-value**
	Diabetic neuropathy	Diabetic without neuropathy	-116.33750*	0.004
		Control	-455.26250*	0.0001
BMI (Kg/m^2)	27.91 ± 0.68	28.90 ± 0.80	27.20 ± 0.95	0.444
Age of subject	59.39 ± 0.99	53.93 ± 1.52	30.80 ± 0.98	0.000*
HbA1C (%)	9.42 ± 0.25	10.40 ± 0.35	5.23 ± 0.05	0.000*

*Correlation is significant at the level of 0.05.

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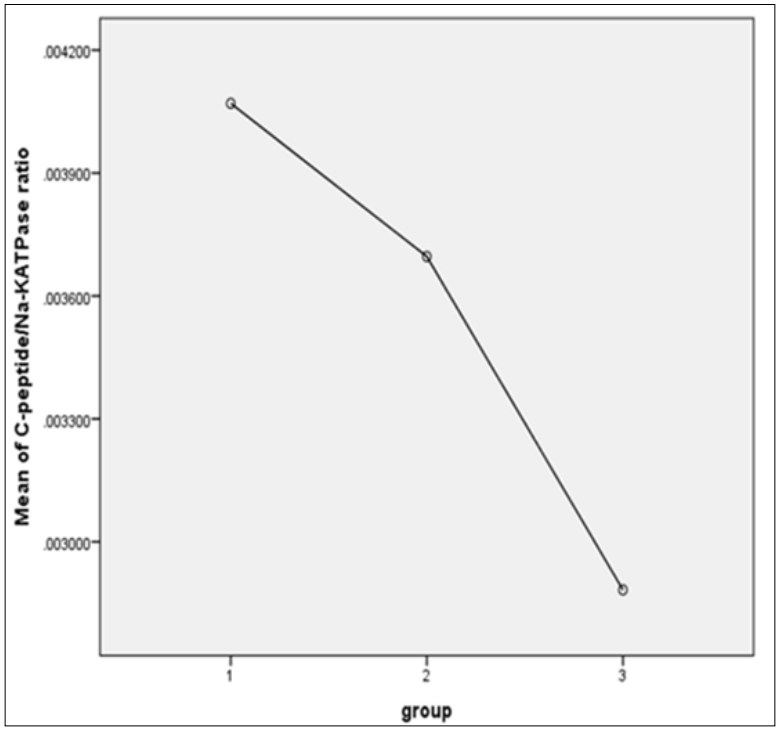

Figure 1.Ratio of Plasma C-peptide/ Erythrocyte Na-K ATPase Activity among Patients, Positive and Negative Controls

Table 3.Seen the correlation of level of C-Peptide(ng/ml) with Duration of Diabetic Mellitus(DM/years), HbA1C(%), Age of subject, and erythrocyte Na-K ATPase activity(*μ*g Pi\g protein)

		Na-K ATPase	C-peptide	HbA1C	BMI	Duration	Age
C-peptide	Pearson correlation	0.032	1	-0.063	0.000	-0.152	-0.177*
	P-value	0.694	1.000	0.447	0.997	0.098	0.030
	N	150	150	150	150	120	150

* Correlation is significant at the 0.05 level (2-tailed).

Discussion

Neuropathy is a serious consequence of diabetes that is linked to several risk factors. This study followed the link between diabetes mellitus duration and diabetic peripheral neuropathy (DPN)[34]. According to our analysis of the Chi-Square Test (Table1), an extended period of disease and age of individuals were substantially linked with diabetic neuropathy, however no relation of BMI with diabetic neuropathy was found. DPN was attributed to poor glycaemic regulator, by way of measured HbA1c, elderly era, and the time of diabetes. Islet function steadily deteriorates as diabetes duration grows, ensuing in lower C-peptide then absorptions of insulin also a higher incidence of DPN.

As a reason, those who ran a separate study to rule out the effects of age and syndrome interval upon the findings. For instance, despite no clear differences in age or diabetes duration across the three categorizes, the C-peptide levels were considerably different.[35]

The levels of plasma C-peptide in diabetic neuropathy (1.17±0.10) were distinguishable from diabetic neuropathy without of neuropathy and control (1.71±0.19) (1.96±0.28) with a p=0.002 in this research,. When there is a question regarding the therapy, C-peptide measurement comes in useful. Much experimental work focused on the probable physiological effects of C-peptide by the method of insulin manufacturing was discovered. Attempts to identify insulin-like effects on blood glucose levels and glucose disposal following glucose loading were unsuccessful. Recently, fresh evidence has been given that demonstrates a particular binding of C-peptide to cell receptors, in conjunction with G-protein. As such a response, in C-peptide defective type diabetic patients, C-peptide can trigger specific intracellular processes and hence alter nerve and kidney function. With the increased use of C-peptide in therapeutic trials, it can be particularly useful in the classification and management of illnesses.[36] Protein kinase C (PKC) and mitogen_activated protein kinase (MAPK) are both engaged by C-pep-

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tide, which elevates Na-K _ATPase_ activity. The activation of the Na-pump is of therapeutic significance since it has been found to be defective in various tissues in persons with type 1 diabetes. Lowered Na-K _ATPase _ activity may lead to decreased nerve conduction velocity, retinal cell dysfunction, reduced endothelial responsibility and reduced microvascular blood flow, renal diseases, and the development of hyperkalaemia due to the key role of Na-K ATPase in the control of intracellular ion concentrations. The impaired Na-K ATPase activity associated through diabetes mellitus and its consequences can be returned to normal with C-peptide injection, albeit the mechanism of this stimulation is unknown.[37] Within our analysis we obtained levels of HbA1C is importantly unusual between three groups : 9.42±0.25, 10.40±0.35, 5.23±0.05 individually by p≤0.001.

HbA1c levels indicate a person's total glycaemic exposure over the previous two to three months. HbA1c 7% is the American Diabetes Association's suggested treatment target for preventing microvascular problems in type 2 diabetes mellitus patients, and it is regarded as the gold standard for glycaemic control monitoring. Excessive HbA1c levels have been linked to subclinical diabetic neuropathy in recent research. These studies, however, are likely restricted since the paper did not adjust for additional risk variables like obesity or dyslipidaemia. The metabolic syndrome includes obesity, dyslipidaemia, and poor insulin tolerance, all of which may have a role in the development of idiopathic neuropathic. Therefore, sole glycaemic management impacts the development of diabetic neuropathy without managing metabolic risk variables may be incorrect.[38] The other trial of the peripheral neuropathy group assessed the relationship from the complication group, contradicting previous findings that suggested a link between high HbA1C and various neuropathies, this may be attributed to the difference in the study design and population.[39] Erythrocyte Na-K ATPase activity is poorer in Type 1 diabetic patients than in control subjects, as we showed in previous studies.[40] When compared to the diabetic group without complications and healthy participants, mean enzymatic activity was lower in the whole group of neuropathy type 2 diabetes patients. Na-K ATPase is a key regulator of intracellular and extracellular cation homeostasis in red blood cells. Changes in this transport enzyme are hypothesized to be associated with hypertension, nephropathy, peripheral neuropathy, and microangiopathy, all of which are consequences of diabetes mellitus. The expansion of the polyol pathway, linoleic acid metabolism abnormalities, protein glycation abnormalities, nerve growth factor abnormalities, and increased generation of oxygen free radicals are among the metabolic processes of diabetes problems. These factors could account for nerve membrane phospholipid pattern disorder and a decrease in Na-K ATPase activity. Both the Na-K-ATPase and the Ca-pumping ATPase in type 2 diabetic's membranes are less functional than the enzymes in normal erythrocytes, which according to evidence.[41] Mean age of subject was 59.39±0.99 yrs in neuropathy class as discriminated with diabetic and control classes 53.93±1.52 yrs, 30.80±0.98 yrs with p≤0.001.

In our experiment, we judged correlation between C-peptide and erythrocyte Na-K ATPase levels was insignificant positive relationship r=.032, p= 0.694. The activity of erythrocyte Na-K ATPase is positively associated with C-peptide concentration, which indicates endogenous insulin production, at the time of sample collection. This enzyme's activity seems to be unaffected by diabetes type or anti-diabetic treatment. Indeed, erythrocyte Na-K ATPase activity is much decreased in Type 2 diabetes individuals on insulin therapy who have extremely low C-peptide than in those with nearly normal fasting C-peptide.[42] On the other hand, correlation between levels of C-peptide with HbA1C(r=-0.063, and duration of diabetes r=-0.152 were unimportantly negative P= 0.447, 0.098 respectively, and negative significantly with age of patients r=-.177, P= 0.030. In this study in order to further clarify the relationship between C-peptide and enzyme activity, we proposed a ratio between these two parameters and studied the statistical significance which showed insignificant regressive relationship between studied groups (Fig 1). Some studies have found potentially devastating relationships between C-peptide levels and diabetes duration, as well as HbA1C levels, confirming the gradual beta-cell degeneration of type-2 diabetes and the link between this decrease and poor metabolic control,[35] but another study by Klein .R. , et al, found no such link.[43] There was no relationship between c-peptide levels and BMI in this investigation as seen in table 3.

Conclusion

According to the findings of the study, a low C-peptide level is linked to diabetic neuropathy. The relationship between C-peptide and the enzyme Na-K ATPase was shown to be insignificantly positive. Furthermore, C-peptide levels in the blood exhibited no correlation with BMI. Slight negative relationships were seen for C-peptide, HbA1c, and duration of illness, even though; there was a substantial negative correlation with age.

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Conflict of Interest: None

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