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ORIGINAL ARTICLE

Circular RNA Cerebellar Degeneration-Related Protein 1 Antisense RNA (Circ-CDR1as) Relative Expression Levels Are Independent Contributors to Insulin Resistance Induced Peripheral Neuropathy

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ABSTRACT

Background: Insulin Resistance IR in sensory neurons may contribute to the development of neurodegeneration. Cerebellar degeneration-related protein 1 antisense RNA (CDR1as) is abundantly expressed in islet cells. Thus, we aimed to investigate CDR1 as relative expression levels in Egyptian patients with IR and to assess its association with risk and severity of peripheral neuropathy (PN).

Methods: The current study conducted on fifty patients with IR (30 patients without PN and 20 patients with PN) and 45 subjects as control group. All research individuals were submitted to clinical and neurological complete examination as well as laboratory and nerve conduction studies. CDR1 mRNA relative expression levels were evaluated by RT-PCR

Results: Among IR patients, there were statistically significant lower values of CDR1 mRNA relative expression levels (0.42±0.31) in PN group compared to IR patients without PN (0.67±0.31) and control group (1.2±0.41). MNCV and CMAP amplitude of median nerve& SNCV and SNAP amplitude of sural and median nerve were significantly decreased in IR patients with PN. There was significant positive correlation between CDR1 mRNA relative expression levels, QUICK, MNCV (median nerve), SNCV (median nerve), CMAP amplitude (median nerve) and SNAP amplitude (median, sural nerve). Among studied parameters, HOMA β, QUICKI, TCSS, CMAP amplitude of median nerve and SNAP amplitude of median nerve were independently correlated with CDR1 mRNA relative expression levels

Conclusion: IR patients with PN had statistically significant lower v alues of CDR1 mRNA relative expression levels than IR patients without PN additionally CDR1 mRNA relative expression levels associated with higher risk of IR and PN.

Keywords: IR; PN, circRNAs; CDR1 mRNA

INTRODUCTION

A status of decreased target tissue(s) responsiveness to circulating normal insulin level, this is the definition of insulin resistance (IR) and consider the cardinal criteria of type 2 diabetes and metabolic syndrome. Both environmental causes (smoking, obesity, lack of exercise, aging and stress) and genetics, all affect the IR development [1]. Even though neurons are not insulin-dependent, they are insulin-responsive [2]. As insulin receptor substrate (IRS) is expressed throughout CNS, peripheral nervous system (PNS) as well as dorsal root ganglion (DRG) neurons [3]

Peripheral neuropathy (PN) is a predominant disorder of the PNS and is considered as a master cause of long-term disability, diabetic polyneuropathy is considered a prime cause of decreased life quality either due to pain, sensory loss,

sensory ataxia, amputation, foot ulcer and fall-related injury **[**4]. PN is characterized by weakness, autonomic changes, and sensory changes. Recent reports demonstrated increased prevalence of PN in patients with prediabetes, and many studies link prediabetes, insulin resistance, obesity and metabolic syndrome to the risk of both diabetic peripheral neuropathy (DPN) [5].

PN molecular mechanisms still mysterious. Recent reports detected the role of epigenetics in pathophysiology of PN. Noncoding RNAs (ncRNAs) including circular RNAs, miRNAs and lncRNAs play an important role in the pathogenesis of PN [6]. CircRNAs called exonic because nearly all of them come from exons gene. CircRNAs was a product of RNA splicing by non-canonical mode [7]. Cerebellar degeneration-related protein 1 antisense RNA (CDR1as [8] acts as a miR-7 sponge and regulates its function. It noteworthy to mention that the main function of CDRlas inhibition of miR-7 expression and increasing the secretion of β-cells in the pancreas [9]. According to experimental study conducted by Memczak et al Cdr1as relative expression levels were overexpressed in midbrain induced developmental defects in Central nervous systems (CNS) [7].

PN are the master of microvascular entanglements and the major contributor to lower limb amputation. Thus, we need for early prediction of PN. This study objective to explore the possible association between of CDR1as relative expression levels in Egyptian patients with IR and to assess its association with risk and severity of PN.

METHODS

This case control study involved 95 participants. Fifty patients suffer from IR and forty-five are healthy controls. Each participant underwent an overall medical history interview, comprehensive clinical evaluation and neurological examination and patients were separated into patients without and with PN (n=30 and 20 respectively). Our study protocol was authorised by the Faculty of Medicine at Zagazig University's ethical committee and the reference number was IRB (Ethics number. 8065), and each participant signed a written informed consent form. Study flowchart is shown in figure 1.

Conventional Nerve Conduction Detection of median, ulnar, and common peroneal nerve (CPNs) motor nerve conduction study (NCS) and the median, ulnar, and sural nerves sensory NCS of all subjects were measured according to Dyck et al. [10].

Ethical Clearance: Written informed consent was obtained from all participants. The study was done according to the present revision of the Helsinki declaration for studies involving humans.

Blood sampling: we measured fasting plasma glucose (FPG), fasting serum insulin (FSI) and calculated IR according to study conducted by Gutch et al [11].

HOMA-IR= Glucose x Insulin/405 Glucose in mass units (mg/dl)

HOMA-IR= Glucose x Insulin/22.5 Glucose in molar units (mmol/L)

Quantitative (qPCR) PCR: Isolation of total RNA from blood using Trizol Reagent (Invitrogen, CA, USA) following the manufacturer's manual. The gene expression was calculated using the 2−ΔΔCt method .GAPDH was used as an endogenous control. The CDR1as primers sequences were: Forward primer :5′ GTGTCTCCAGTGTATCGGCG-3′, and reverse primer: 5′TACTGGCACCACTGGAAACC-3′. Regards, GAPDH primers sequences were: Forward primer :5′ GTCGGTGTGAACGGATTTG-3′, and reverse primer: 5′GAATTTGCCGTGAGTGGAG-3′.

Statistical analysis

Statistical Package was used in statistical analysis for the social sciences for windows (26.0 version; SPSS Inc., Chicago, IL, USA). Data were expressed using descriptive statistic (mean ± standard deviation) and were analyzed using "t" test. Pearson correlation coefficient was used to assess the association between CDR1 mRNA relative expression levels with TCSS, nerve amplitude and nerve conduction velocity.

The potential accuracy of CDR1 mRNA relative expression levels was assessed by Receiver operating characteristic (ROC), area under the curve (AUC), and the cutoff values for diagnosis of PN among IR patients. We considered *P* to be significant at <0.05 with a 95% confidence interval (CI).

3. Results

Among studied subjects, in the IR patients with PN group(n=20), 64 % were female and 36% were male, While IR patients without PN(n=30) 65% were female and 35% were male. In control group (n=45) , 63% were female and 37% were male. The studied groups were matched for age, sex and smoking.

3.1. Clinical and laboratory findings of examined participants.

There were significant higher values in the IR patients with PN group compared to IR patients

without PN and control group regards hypertension, anthropometric indices, dyslipidemia, IR and TCSS .On the other hand , IR patients with PN had significantly lower values of HDL and QUICKI compared IR patients without PN and control group as shown in table 1*(P* < 0.001).

3.2. CDR1 mRNA relative expression levels in the studied groups.

Our results show that IR patients with PN had statistically significant lower values of CDR1 mRNA relative expression levels (0.42±0.31) compared to IR patients without PN (0.67±0.31) and control group (1.2±0.41) as shown in table 1.

3.3. **Electrophysiological tests**

For accurate assessment of neuropathy, we tested our patients by electrophysiological tests, and we found that MNCV of median nerve was significantly decreased in IR patients with PN compared to another group, (p < 0.001). Moreover, SNCV of sural and median nerve were significantly decreased (*p* < 0.001). While, CMAP amplitude of median as well as SNAP amplitude in sural and median nerve were significantly decreased in IR patients with PN compared to another group (p < 0.001),table 2.

3.4. Correlations between CDR1 mRNA relative expression levels with TCSS, among IR patients with PN

The current research detected positive association between CDR1 mRNA relative expression levels and QUICKI, MNCV (median nerve), SNCV (median nerve), CMAP amplitude (median nerve) and SNAP amplitude (median, sural nerve). However, the negative observed association were with HOMA-IR, HOMA β, HbA1c and TCSS (P<0.001) (Table 3). To gain further insights, we performed linear regression test to evaluate the most independent associated with CDR1 mRNA we applied linear regression analyses and we found that, among studied parameters, only HOMA β, QUICKI, TCSS, CMAP amplitude of median nerve and SNAP amplitude of median nerve were associated. **(P<0.001) (Table4).**

3.5. The power of CDR1 mRNA for distinguishing IR patients from control group.

We investigated the potential diagnostic value of CDR1 mRNA by ROC test (**Fig. 2).** When we discriminate IR patients from control, the cutoff values of CDR1 mRNA relative expression levels were 1.039 and the AUC were 0.901(0.831-0.971) , furthermore, the sensitivities and the specificities were (98.2% and 84.2%).

3.7. The accuracy of CDR1 mRNA for diagnosis PN among IR patients

The power of CDR1 mRNA relative expression levels by ROC test (**Fig. 3).** We detected that, the cutoff values of CDR1 mRNA relative expression values were 0.64 and the AUC were 0.888(0.769-1.000). moreover, the sensitivities and the specificities were (88% and 67.3%).

Table 1:Clinical and laboratory characteristics of the studied groups.

Variables	Control group (*n* =45)	IR patients without PN (*n* =30)	IR patients with PN (*n* =20)	*P* value
Age (years)	42.9±8.7	43.1±7.4	45.1±4.4	0.259
Systolic blood pressure (mm Hg)	124.2±22.8	156.5±25.4	159.5±11.4	<0.001*
Diastolic blood pressure (mm Hg)	76.26±5.7	84.8±7.8	104.8±8.8	<0.001*
Waist /hip ratio	0.86±0.9	0.94±0.59	1.29±0.3	<0.001*
Body mass index (kg/m^2)	22.8±5.9	33.03±5.6	37.3±8.96	<0.001*
TC (mg/dL)	188.8±14.6	214.5±34.3	233.5±31.2	<0.001*
TG (mg/dL)	143.2±23.04	194.8±46.02	194.8±46.02	<0.001*
LDL (mg/dL)	76.5±22.4	113.39±30.4	130.5±21.6	<0.001*
HDL (mg/dL)	54.7±5.6	37.9±6.2	32.9±9.2	<0.001*
FPG (mg/dL)	83.2±8. 2	84.3±2.5	85.6±2.1	<0.001*
FSI (µU/mL)	7.2±2.9	29.26±5.2	36.26±6.2	<0.001*
HOMA-IR	1.1±0.9	6.45±2.7	8.45±2.3	<0.001*
HOMA β	88.2 ± 22.6	107.3±37.4	116.2±28.5	<0.001*

Variables	Control group (*n* =45)	IR patients without PN (*n* =30)	IR patients with PN (*n* =20)	*P* value
QUICKI	0.51±0.14	0.35.1±0.18	0.32.1±0.19	<0.001*
HbA1c (%)	5.51±0.31	5.93±0.45	6.03±0.5	<0.001*
TCSS	1.5±0.21	6.14 ± 2.6	8.14 ± 2.6	<0.001*
CDR1 mRNA relative expression levels	1.2±0.41	0.67±0.31	0.42±0.31	<0.001*

PN, peripheral neuropathy ;IR: insulin resistance ;HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessments of insulin resistance; HOMA-β, an index of β-cell function; QUICKI, quantitative insulin sensitivity check index; BMI, body mass index; FSI ,fasting serum insulin; FPG, fasting plasma glucose ; HOMA-IR, homeostasis model assessments of insulin resistance; Circ-CDR1as, circular RNA cerebellar degeneration-related protein 1 antisense (TCSS, Toronto Clinical Scoring System.* P < 0.05 when compared with control group.

Table 2: Electrophysiological tests among studied groups

Electrophysiological tests	IR patients without PN (*n* =30)	IR patients with PN (*n* =20)	P-value
MNCV (m/s)			
Median	47.8±10.92	42.66±4.11	<0.001*
Ulnar	48.16±5.54	47.13±6.47	0.085
CPN	47.53±6.76	48.8±5.81	0.084
PTN	46.44±7.76	47.8±5.23	0.073
SNCV (m/s)			
Sural	43.41±8.32	34.2±2.61	<0.001*
Median	48.1±5.42	41.9±6.22	<0.001*
Ulnar	43.6±7.82	44.8±4.72	0.066
CMAP amplitude (mV)			
Median	6.25±1.67	4.93±1.5	<0.001*
Ulnar	6.25±1.74	5.93±1.21	0.095
CPN	6.38±1.26	6.56±0.61	0.224
PTN	7.36±1.69	7.54±0.31	0.513
SNAP amplitude (*μ*V)			
Sural	5.18±2.71	3.79±1.22	<0.001*
Median	8.77±2.12	5.9±1.19	<0.001*
Ulnar	5.68±1.67	5.19±1.38	0.120

MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity; CPN, common peroneal nerve; PTN, posterior tibial nerve; CMAP, compound muscle action potential; SNAP, sensory nerve action potential.* P< 0.05

Table3 Pearson correlation coefficient between CDR1 mRNA relative expression levels with other studied parameters among IR patients with PN.

Variables	IR patients with PN (*n* =20)	
	r	p
Systolic blood pressure (mm Hg)	264-0.	0.052
Diastolic blood pressure (mm Hg)	-0.247	0.070
Waist /hip ratio	-0.159	0.051
Body mass index (kg/m^2)	-0.272	0.045

Variables	IR patients with PN (*n* =20)	
	r	p
HOMA-IR	-0.466	<0.001*
HOMA β	-0.521	<0.001*
QUICKI	0.471	<0.001*
HbA1c (%)	-0.367	<0.001*
TCSS	-0.722	<0.001*
MNCV		
Median	0.756	<0.001*
Ulnar	0.185	0.176
CPN	0.063	0.412
PTN	0.115	0.304
SNCV		
Sural	0.130	0.344
Median	0.694	<0.001*
Ulnar	0.104	0.394
CMAP amplitude		
Median	0.694	<0.001*
Ulnar	0.012	0.122
CPN	0.016	0.125
PTN	0.113	0.393
SNAP amplitude		
Sural	0.674	<0.001*
Median	0.753	<0.001*
Ulnar	0.053	0.691

Table 4: Linear regression analyses in IR patients with PN to test the influences of the main independent variables against CDR1 mRNA relative expression levels (dependent variable).

Model	Unstandardized Coefficients		Standardized Coefficients	t	p	95% C.I.	
	B	SE	Beta			Lower Bound	Upper Bound
Constant	2.636	1.322		1.995	.052	-0.018	5.291
HOMA-IR	0.020	0.024	0.104	0.847	0.401	-0.028	0.068
HOMA β	-0.010	0.005	-0.266	-2.164	<0.001*	-0.019	-0.001
QUICKI	1.991	0.516	0.464	3.856	<0.001*	0.954	3.028
TCSS	0.817	0.190	0.422	4.299	<0.001*	1.192	0.442
MNCV of Median N.	0.008	0.006	0.102	1.335	0.184	0.004	0.019
SNCV of Median N.	-0.295	0.188	-0.188	-1.572	0.122	-0.673	0.082
CMAP amplitude of Median N.	0.028	0.004	0.551	6.946	<0.001*	0.020	0.036
SNAP amplitude of Median N.	0.012	0.002	0.466	4.815	<0.001*	0.007	0.016

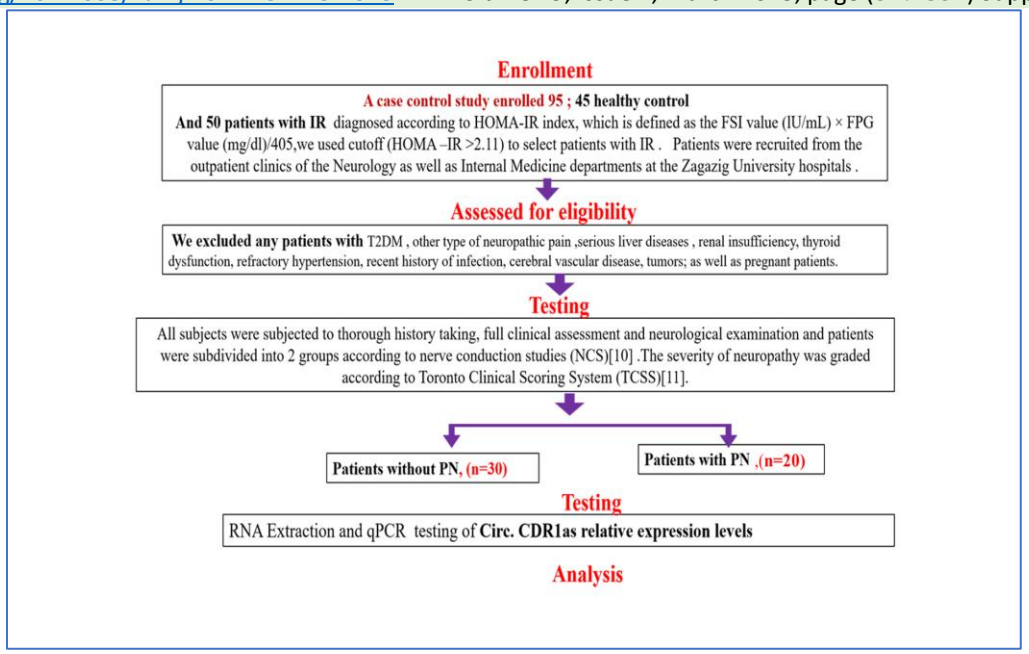

Figure (1): flowchart of the study

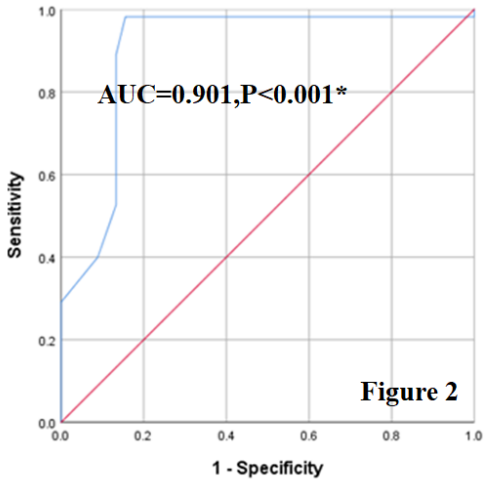

Figure (2): the accuracy of Circ. CDR1as relative expression levels for discriminating IR patients from control group by ROC analysis

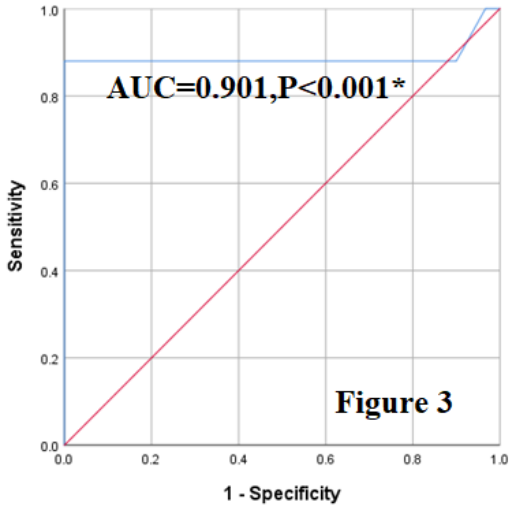

Figure (3): the accuracy of Circ. CDR1as relative expression levels for discriminating PN among studied patients by ROC analysis

4.DISCUSSION

The current research was conducted on 45 control group and 50 patients with IR. among IR group ,20 patients had PN as diagnosed by neurological examination and confirmed by nerve conduction study. As expected, patients with IR and PN had significant cardiovascular risk factors compared to IR patients without PN Regards nerve conduction study, MNCV and CMAP amplitude were significantly decreased in IR patients with PN compared to IR patients without PN. while SNCV and SNAP amplitude of sural and median nerve were significantly decreased in IR patients with PN compared to IR patients without PN while all other nerve velocities difference nerve amplitudes were not significant.

There is growing evidence that genetic and epigenetic markers could have diagnostic, prognostic and therapeutic properties. However, there is often uncertainty about the genetic basis of PN in IR patients. Thus, the aim of the current research was to elucidate CDR1as relative expression levels in Egyptian patients with IR and to assess its association with risk and severity of PN. Nonetheless, there is evidence that, one of the circRNAs, Cdr1as dysregulation leads to midbrain developmental damage, which was comparable to the miR-7[7]. Interesting findings of Pollock et al detected that the development of cerebral cortex is regulated by microRNA-7 through the p53 pathway [12]. Circ-CDR1as, also known as ciRS-7, a preponderance of evidence suggests that is Circ-CDR1as profoundly implicated in the cellular biological pathway, according to Mao et al. results, angiogenesis and activity of endothelium were suppressed by CircCDR1 [13]. Furthermore, mounting evidence reveals that circ-CDR1as additionally aggravated inflammatory responses [14].

In study conducted by Wang and Wang study observed that hippocampal neuronal were protected by dexmedetomidine therapy, it is associated with downregulation expression of circ-CDR1. While overhead expression of circ-CDR1 could be weaken the dexmedetomidine protection on H/R-induced inflammation and apoptosis in HT-22 cells. [15].

Recently published studies highlighted the relative expression levels of miR-7 as major islet microRNA [16]. Also, the results of Correa-Medina et al. showed that miR-7 is specially expressed in beta cell of pancreas [17]. In addition, interesting study revealed that proliferation and mTOR pathway controlled by MicroRNA-7 in adult island of pancreas [18].

The interesting result of this research was that there were statistically significant lower values of CDR1 mRNA in IR patients with PN compared to other groups. We in this study attempted to pierce out the association between CDR1 mRNA relative expression levels Our results demonstrated significant positive correlation between CDR1 mRNA relative expression levels and QUICKI, MNCV (median nerve), SNCV (median nerve) , CMAP amplitude(median nerve) and SNAP amplitude(median, sural nerve) .

Interestingly, CDR1 mRNA relative expression levels were significantly negative correlated with HOMA-IR, HOMA β, HbA1c and TCSS. Even more important, among studied parameters, only HOMA β, QUICKI, TCSS as well as CMAP and SNAP amplitude of median nerve were independently correlated with CDR1 mRNA relative expression levels.

In a recent comprehensive study, Latreille et al they suggested that miR-could regulates β cell function via controlling epigenetic regulate insulin functions Additionally, lower expression of miR-7 in obesity leads to increase regeneration of β cell and pancreatic action .[19].

To evaluate the probable diagnostic benefit of CDR1 mRNA relative expression in discrimination IR patients from control, we detected that the AUC were 0.901 and the sensitivity was 98.2% and specificity was 84.2%. Interestingly, the possible diagnostic value of CDR1 mRNA relative expression in discernment PN among IR patients, we found that the AUC were 0.888 and the sensitivity was 88% and specificity was 67.3%. Substantial evidence implicate IR seems to be associated with PN independent of blood glucose level.

The strength of the current study. This study has several unique strengths. It is the first Egyptian study ever published aiming to investigate whether CDR1 as relative expression levels could be used as diagnostic marker of PN in IR patients. The diagnosis of PN based on nerve conduction study in addition clinical and neurological examinations. **The limitation of our study** is that it included only Egyptians, and therefore, it remains unclear whether our findings are applicable to other ethnic groups

CONCLUSION

The CDR1 mRNA relative expression levels were downregulated in IR patients with PN compared to another group. Additionally, CDR1 mRNA relative expression levels associated with higher risk of IR and PN. The identification optimum cut-off of serum CDR1 mRNA relative expression levels could help in evaluating IR patients with PN .

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