Studying The Association Of Metformin Dose With Peripheral Neuropathy In Diabetic Patients At Jordanian Royal Medical Services

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Abstract

The aim of the present study was to study the association of metformin dose with peripheral neuropathy in diabetic patients at Jordanian Royal Medical Services. A retrospective study was conducted to collect data from files of 392 diabetic patients at Jordanian Royal Medical Services. A working sheet was created for each patient that included the following information: gender, age, peripheral neuropathy, vitamin B12 status, metformin use, and metformin dose. Data were analyzed using SPSS version 20. Data were represented as frequencies and percentages for categorical variables such as gender, and vitamin B12 status; means and standard deviations for continuous variables such as age. The relationships between variables were examined using Chi-Square, and One Way Anova. Significance was considered at alpha level <0.05. Study findings showed that the prevalence of diabetic peripheral neuropathy among participants was about 43%. Vitamin B12 deficiency was about 7%. Diabetic peripheral neuropathy was significantly associated with gender (p=0.018). No significant associations were observed between peripheral neuropathy and vitamin B12 or metformin dose. Taken together, the results of the present study showed that treatment with metformin did not lead to vitamin B12 deficiency, although the prevalence of diabetic peripheral neuropathy was relatively high (about 43%).

Keywords: Peripheral neuropathy, diabetes, vitamin B12, metformin

Introduction

Type 2 diabetes mellitus (DM) is considered as one of the most prevalent metabolic diseases at global level, and its prevalence is likely to with age and obesity (Butterfield et al., 2014). The functions of several organs are deteriorated by DM such as brain (Arnold et al., 2014).

Metformin is used widely as anti-diabetic drug (Ruggiero-Lopez et al., 1999; Kirpichnikov etal.,2002; Yamagishi et al., 2008; Ma et al., 2015). It acts through lowering glucose hepatic production (Derosa et al., 2008). Although the mechanisms of metformin action are not well clear, it has been recently suggested that to some pleiotropic actions (Chen et al., 2001). Among these actions is AMP-activated protein kinase (AMPK) (Steinberg and Kemp, 2009). Several roles of AMPK have been involved in DM, neuroprotection, anti-inflammation and alteration of oxidative stress (Chakraborty et al., 2011; Salminen et al., 2011).

It has been indicated to the possibility of inhibition of injury-induced neuropathic pain (Melemedjian etal.,2011). In another study, metformin was able to reverse mechanical allodynia in lumbar radiculopathy pain in experimental models such as rats and mice (Taylor et al.,2013). Furthermore, using mouse model showed the potential of metformin to offer protection against chemotherapy induced neuropathic pain (Mao-Yingetal.,2014).

Other studies showed that long term treatment by metformin lowers serum concentration of cyanocobalamine up to 30%, and this may occur in approximately in 30% of treated patients (Mazokopakis and Starakis, 2012). This process depends on inhibition of cyanocobalamine intrinsic factor complex absorption, which depends on calcium, so that it can be treated with calcium supplementation (Jager et al., 2010). It has been demonstrated that the treatment of metformin is not likely to cause megaloblastic anemia except in cases of heavily doses over a long duration (Mazokopakis and Starakis, 2012).

Study objectives

To study the association of metformin dose with peripheral neuropathy in diabetic patients at Jordanian Royal Medical Services.

Methods and subjects

This section includes the methods of choice which were involved to collect data and to conduct the appropriate statistical analyses.

Study design and setting

A retrospective design was employed to collect data from study participants. The study was conducted at Jordanian Royal Medical Services.

Study sample

Study sample included a total of 392 diabetic patients.

Data collection

A working sheet for each diabetic patient was created for each diabetic patient. The required information were extracted from files of patients including age, gender, peripheral neuropathy, metformin use, metformin dose, and the status of vitamin B12.

Data analysis

All data were entered into excel sheet to obtain the raw data. SPSS version 20 was used to analyze data. Categorical variables such as gender were presented as frequencies and percentages, while continuous variables such as age was presented as mean and standard deviation. The relationships between variables were examined using Chi-Square, T test, and One Way Anova. Significance was considered at alpha level ≤ 0.05.

Results

General characteristic of participants

As it can be demonstrated in table 1, the mean age of study participants was 56.18+9.51 years. About 47% were males. The prevalence of peripheral neuropathy was approximately 43%. About 85% of diabetic patients received metformin treatment, and the mean metformin dose was 1474.68+906.78 mg/day. Vitamin B12 deficiency was shown among about 7% of patients.

Table 1: General characteristic of participants

Variable	Description
Age (M±SD) years	56.18±9.51
Gender (N, %):	
Males	183 (46.7%)
Females	209 (53.3%)
Peripheral neuropathy(N, %):	
Yes	168 (42.9%)
No	224 (57.1%)
Metformin (N, %):	
Yes	331 (84.6%)
No	61 (15.6%)
Metformin dose (M±SD) mg	1474.68±906.78
Vitamin B12 (N, %):	
Deficiency	26 (6.6%)
Normal	366 (93.4%)

The relationship between peripheral neuropathy and study variables

As it can be seen in table 2, male were more likely to develop peripheral neuropathy than females, and this variation was statistically significant (p=0.018). No significant variations were observed between peripheral neuropathy and each of metformin use (p=0.780) and vitamin B12 status (p=0.446).

Table 2: The relationship between peripheral neuropathy and study variables

Variable	Peripheral neuropathy				P value
	Yes		No		
	N	%	N	%	
Gender					0.018
Males	90	49.2	93	50.8	
Females	78	37.3	131	62.7	
Metformin use					0.780
No	143	43.2	188	56.8	
Yes	25	41	36	59	
Vitamin B12					0.446
Normal	13	50	13	50	
Deficiency	155	42.3	211	57.7	

The effects of study variables on peripheral neuropathy

In this section, One Way Anova was conducted to examine the effects of study variables on peripheral neuropathy. As it can be illustrated in table 3, the following variables were examined: age, gender, metformin, metformin dose, and vitamin B2. Among these variables, gender was significantly associated with peripheral neuropathy (p=0.018), while the remaining variables were not statistically associated significantly with peripheral neuropathy (p>0.05).

Table 3: The effects of study variables on peripheral neuropathy

Variable	Sum of squares	DF	Mean square	F	P-value
Age	46.14	1	46.164	0.510	0.476
Gender	1.395	1	1.395	5.66	0.018
Metformin	0.014	1	0.014	0.103	0.748
Metformin dose	368333.466	1	368333.466	0.447	0.504
Vitamin B12	.036	1	.036	0.578	0.448

Discussion

The present study showed that the prevalence of peripheral neuropathy among diabetic patients was about 43%. The prevalence of peripheral neuropathy in other studies such as the study of Davies et al (2006) in which the prevalence of peripheral neuropathy was 26.4%. other studies reported the prevalence of peripheral neuropathy to vary from 3% (Sorensen, Molyneaux and, Yue, 2002) to 32% (Ziegler etal., 1993).

The findings of our study showed that vitamin B12 deficiency was about 93% among diabetic patients. Reviewing the literature showed that the prevalence of vitamin B12 deficiency varied from 5.8% to 33% (Pflipsen et al., 2009; Qureshi, Ainsworth, and Winocour, 2011; Reinstatler et al., 2012).

The findings of the present study revealed a significant role of gender to develop peripheral neuropathy (p=0.018). This finding is not consistent with the results of the study of Kodali, Seshaiah, and Kumar (1990) who found higher prevalence of peripheral neuropathy among women compared with men.

No significant association was found between diabetic peripheral neuropathy and vitamin B12 deficiency and metformin (p>0.05). We think, based on these findings, that metformin provides neuroprotection and confirm other studies such as Chakraborty et al (2011) and; Salminen et al (2011).

Conclusion

The results of the present study showed that treatment with metformin does not lead to vitamin B12 deficiency, although the prevalence of diabetic peripheral neuropathy was relatively high (about 43%). Diabetic peripheral neuropathy was significantly associated with gender (p=0.018).

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