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Association of Low Serum Magnesium Levels in Type 2 Diabetes Mellitus with & without Hypertension

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Abstract

Background: Diabetes Mellitus is a widespread metabolic abnormality that constitutes a most important physical dilemma in the world. Hypomagnesaemia accelerates the rate of diabetic complications. **Objective:** To analyze the association of magnesium levels in DM (Type 2 Diabetes Mellitus) with and without complication of Hypertension. **Design:** It was a comparative analytical study. **Setting:** This research was carried out in medicine department, Peoples Medical College Hospital, Nawabshah from March 2016 to February 2017. **Samples:** 245 patients with Type 2 DM after fulfilling the selection criteria were included, out of them **123** with hypertension and **122** without hypertension. **Methods:** After a short-lived consultation, all the subjects were categorized for variable analyses like age, gender, Type 2 DM with and without hypertension, duration of diabetes and presence of hypomagnesaemia. Joint National Committee (JNC 8) classification of Hypertension was applied to collect data. Blood samples were drawn for research purpose in fasting state for serum magnesium level analyses on the basis of hypertension and without hypertension. **Results:** In **245** diagnosed Type 2 diabetic patients, **160** were males and **85** were females. Out of them, 123 were hypertensive while 122 were non hypertensive. Normal magnesium was present in 120 (48.97%) and low magnesium was present in 125 (51.02%) patients overall. A decreased serum level of magnesium was observed in 52.04% hypertensive subjects with diabetes and 50% non-hypertensive subjects with diabetes. **Conclusion:** Frequency of decreased serum magnesium is widespread in T2DM with and

without hypertension.

Keywords

Type 2 Diabetes Mellitus, Hypertension, Magnesium, Hypomagnesaemia

1. Introduction

Diabetes Mellitus is a universal metabolic disorder increasing morbidity and mortality since centuries. It manifests as disturbed metabolism with raised blood sugar due to absolute or relative deficiency or resistance to insulin [1]. In 2010, round about 280 million human beings worldwide were with diabetes, and this number of diabetic cases would reach up to 438 million by 2030 [2]. 1.1 million people died due to diabetes in 2005, and this will double through 2005 and 2030 [3]. A cross survey conducted in rural and urban areas of Pakistan showed 19% prevalence of diabetes mellitus [4]. Approximately 90% - 95% of all diagnosed diabetes cases are due to T2DM [5]. Magnesium is the fourth most copious cation found generally and is present abundantly as intracellular cation [6]. Magnesium is very essential for body. When its levels are decreased (Hypomagnesemia), it can interrupt most of organ systems and can be reason for deadly outcomes such as arrhythmias (ventricular), vasospasm of cardiac arteries or may result in unexpected death. Magnesium had also been known as "forgotten cation" which is a well-known element, and increased and decreased levels had been observed in sick subjects [7] [8] [9]. Hypomagnesemia plays role in resistance of insulin, hypertension, diabetes mellitus and dyslipidemias. A noteworthy relationship was reported among hypomagnesemia and diabetes mellitus (DM2) in ARIC study. Furthermore, Mg depletion may also affect the onset and progression of chronic diabetic complications [10]. Magnesium was used in the treatment of pre-eclampia and eclampsia syndromes ever since 19th century. Association amongst blood pressure and magnesium had been reported in different researches. Hypomagnesaemia causes vasoconstriction leading to hypertension. It was reported that magnesium intake causes decrease in blood pressure [11] [12] [13] [14] [15]. Many studies had been conducted internationally. In them, it was described that lower magnesium levels were associated with diabetes and hypertension but few studies here.

The rationale of current research was to assess serum Magnesium and its relationship with Diabetes Mellitus (T2DM) subjects with as well as without hypertension. Exact identification and proper management can to a great extent decrease the morbidity and mortality pace in the human race.

2. Patients and Methods

2.1. Operational Definitions

Diagnosis of Hypomagnesaemia [16]

Cutoff values for serum Magnesium levels

- Normal plasma Mg: 1.5 - 2.5 mEq/L.
- Hypomagnesaemia: <1.5 mEq/L.
- Hypremagnesaemia: >2.5 mEq/L.

Diagnosis of DM type [17]

Type 2 DM diagnosed through clinical history, examination and investigations and OHA and insulin, medical records and according American Diabetic Association Criteria.

1) FBS values of >126 mg/dL on two separate occasions.

2) 02 hours Post prandial Glucose ≥200 mg/dL (11.1 mmol/L) during OGTT (75-g)

3) Symptomatic patients, RBS of >200 mg/dL suggests diabetes.

4) A1C ≥ 6.5% (48 mmol/mol).

Diagnosis of hypertension [18]

Vascular complication Hypertension, was diagnosed on medical history, clinical examination and blood pressure monitoring, blood pressure <139/89 mmHg normal and >140/90 mmHg hypertension.

2.2. Data Collection

This was case controlled, comparative and analytical study. Duration of study was 01 year from March 2016 to February 2017. This is a hospital-based study in which 245 subjects of T2DM that visited/admitted in Medical Departments at PUMHS Nawabshah. The patients in this study were included on basis of History, Clinical Examination and Laboratory investigations (laboratory evaluation of Mg). Venous blood samples collected from 245 male and female subjects with T2DM with and without high blood pressure. Rao-software for sample size calculation was used with sample size 245 subjects with margin of error 5.25%. Blood samples collected were stored prior to analysis. Automatic Analyzer was used to determine total serum Magnesium. Convenience/purposive sampling technique were used. This hospital based study was targeted to those patients with age more than 40 years and diagnosed cases of type 2 DM with and without Hypertension were included. Patients with acute and chronic complications of diabetes mellitus such as diabetic keto-acidosis, lactic-acidosis, Non-Ketotic Hyperosmolar Coma, Hypoglycemia, Neuropathy, Nephropathy and retinopathy were excluded. Patients on dialysis, drugs like diuretics or containing Magnesium, extra supplementation of Magnesium, Alcoholic and Smokers, Diabetes Mellitus secondary to other diseases like Cushing syndrome, Acromegaly, and also Gestational Diabetes were excluded.

2.3. Statistical Analysis

Data was analyzed by using SPSS 20.0. Frequency & percentage were computed for categorical variables like gender, and hypomagnesaemia. Mean and standard deviation calculated for variables (quantitative) as age. Magnesium significance was seen in type 2 DM in relation to age, gender, with HTN, without HTN, du-

ration of T2 DM, FBS and RBS, HBA1c and BMI to see the impact on outcomes.

3. Results

There were 245 diabetic subjects, out of them 123 were hypertensive while 122 were non-hypertensive.

3.1. Quantitative Variable Analyses

The mean age of study patients was 57.02 with standard deviation of 6.32 years; minimum age was 45 years while maximum was 75 years ($P < 0.000$). The mean systolic blood pressure was 145.55 with SD 29.54, minimum 110 mmHg and maximum 235 mmHg ($P < 0.000$). The mean diastolic blood pressure was 89.22 with SD 13.08, minimum 70 mmHg and maximum 120 mmHg ($P < 0.000$). The mean FBS level was 126.15 mg/dl with SD 24.02, minimum 85 mg/dl and maximum 195 mg/dl ($P < 0.033$). The mean RBS level was 277.46 mg/dl with SD 59.45, minimum 190 mg/dl and maximum 410 mg/dl ($P < 0.000$). The mean serum magnesium level was 1.52 mg/dl with SD 0.37, minimum 1 mg/dl and maximum 2.4 mg/dl ($P < 0.000$). The mean HbA1c level was 9.64% with SD 1.62, minimum 7% and maximum 13.00% ($P < 0.000$). Most of the diabetic patients were with duration of 5 - 10 years, while in BMI over weight population was dominant. Significant statistical values are shown in Table 1.

3.2. Demographic Qualitative Variable Analyses

The study population consisted of 160 (65.3%) male and 85 (34.7%) were female subjects. Regarding the socio-demographic profile 94.7% were married and 5.3% were unmarried. A large number 75.9% were from rural areas and 24.1% belonged to urban community. Majority of subjects with hypomagnesaemia were illiterate. In current study majority of subjects were manual workers 34.3%, most of females 25.7% were house wife, 24.1% did not satisfy any occupation and 15.9% subjects were office workers. As for socio economic status of subjects concerned [(Income < Rs: 20,000/m (lower income class/Poor Peoples), Income <Rs - 27,000 (middle income class) and Income > Rs 28,000 (middle upper income class)], 209 (85.3%) belonged to poor back ground, 29 (11.8%) were middle class and 7 (2.9%) belonged to upper class (Figure 1).

Oral hypoglycemic drugs were used by 68.2%, insulin in 10.9% and rest of patients (21.2%) did not use any medication, and drug compliance was unsatisfactory

Table 1. Statistics analysis of different variables, n = 245.

	Age In Years	Duration of Diabetes	Blood Pressure Systolic	Blood Pressure Diastolic	BMI	FBS	RBS	Level of magnesium	HBA1c
Mean	57.0245	1.6082	145.5510	89.2245	1.4490	126.1551	277.4612	1.5249	9.6424
Std. Deviation	6.32645	0.71398	29.54578	13.08119	0.56761	24.02663	59.45996	0.37416	1.62962
p-value	0.000	0.000	0.000	0.000	0.000	0.033	0.000	0.000	0.000

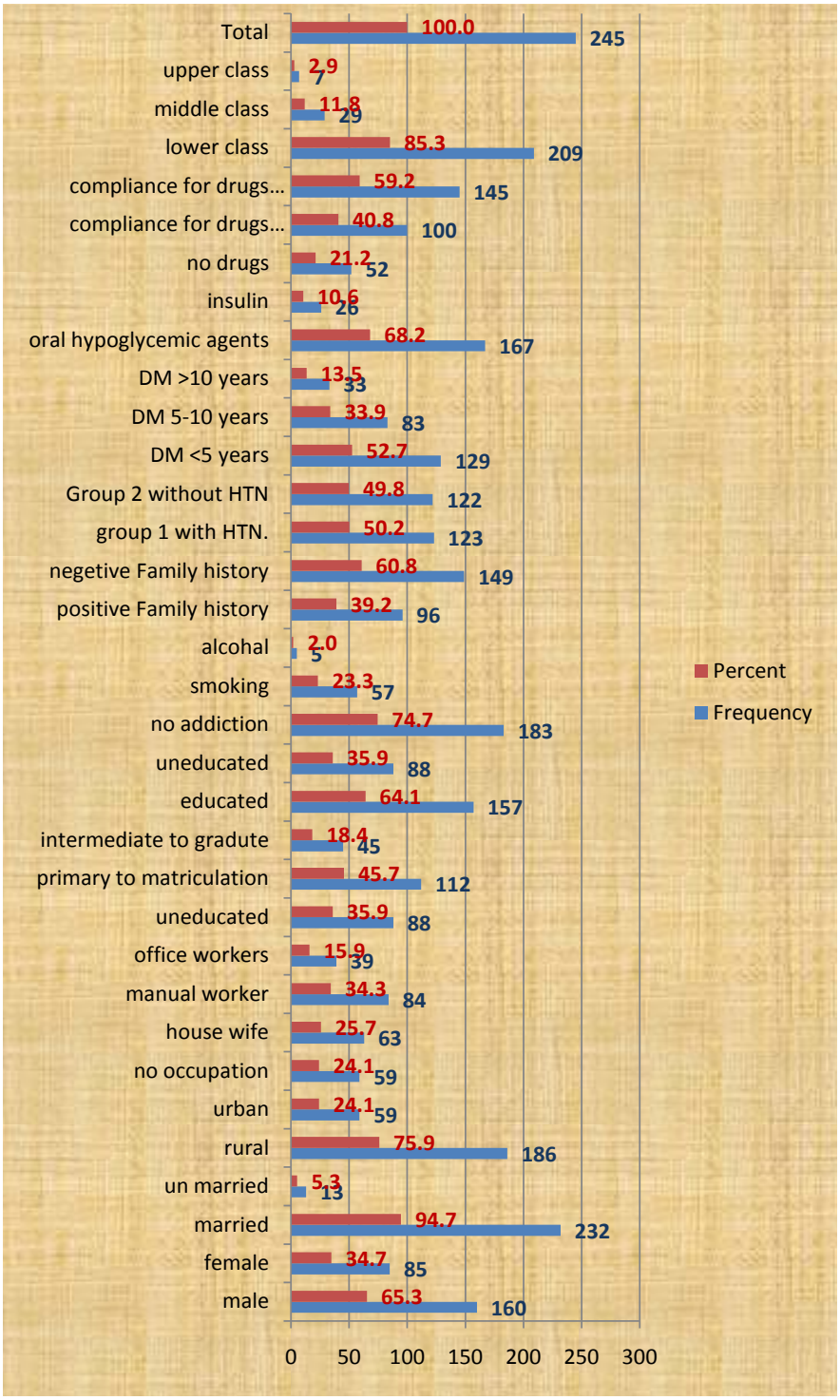

Figure 1. Demographic variables, n = 245.

in 145 (59.2%) patients. Hypertension was associated in 123 (50.2%) diabetic subjects. A positive family history of DM was obtained in 96 (39.2%) subjects. DM was seen in 129 (52.7%), 83 (33.9%) and 33 (13.5%) subjects with duration of <5, 5 - 10 and >10 years respectively. All the statistical variables were with significant P value (0.000) (**Figure 1**).

3.3. Diabetes Hypertension & Magnesium Statistical Analyses

Low serum magnesium was found in total 125 (51.2%) subjects with T2DM. From 123 subjects with hypertension 59 (47.96%) were with normal magnesium while 64 (52.04%) were with low magnesium. From 122 non hypertensive patients 61 (50%) were with normal magnesium level while 61 (50%) were with low serum magnesium levels.

Normal magnesium was present in 120 (48.97%) patients, 79 (65.8%) male out of them 39 (32.5%) in group 1 with HTN & 40 (33.3%) without HTN in group 2 and out of 41 (34.2%) female patients 20 (16.7%) in group 1 with HTN & 21 (17.5%) without HTN in group 2. Low magnesium was found in 125 (51.02%) patients, out of them 81 (64.8%) were male, 47 (37.6%) with HTN in group1& 34 (27.2%) without HTN in group 2. Out of 44 (35.2%) female patients 17 (13.6%) were with HTN in group 1 & 27 (21.6%) without HTN in group 2 (**Table 2**).

Chi-square test was applied for frequency and odds ratio to verify the potency of correlation. P = 0.038 in our study population in relation to hypomagnesaemia. Different chi-square was performed showing important statistical values. The odds ratio calculated was 1.0847, with 95% confidence Interval 0.6572 to 1.7904, with significance level P = 0.7503.

Number of valid cases in group 1 was 120 with normal serum magnesium level (1.5 - 2.5 meq/dl) and Pearson Chi-Square Value was 0.004 with df 1, Asymp. Sig. (2-sided) 0.951. The Continuity Correction Value was 0.000, with df 1and Asymp. Sig. (2-sided) 1.000. The likelihood ratio was 0.004 with df 1 and Asymp. Sig. (2-sided) 0.951. Fisher's Exact Test shows the Exact Sig. (2-sided) 1.000 and Exact Sig. (1-sided) 0.552. Linear by linear association value was 0.004 with df 1 and Asymp. Sig. (2-sided) 0.004. with point of probability 0.152.

Number of valid cases in group 02 were 125 with hypomagnesemia (<1.5 meq/dl) and Pearson Chi-Square Value was 4.290 with df 1 and Asymp. Sig. (2-sided) 0.038. Continuity Correction Value was 3.549 with df 1 and Asymp. Sig. (2-sided) 0.060. The likelihood ratio was 4.316 with df 1 and Asymp. Sig. (2-sided) value 0.038. Fisher's Exact Test had shown Exact Sig. (2-sided) value 0.042 and Exact Sig. (1-sided) value 0.030. Linear by linear association value was 4.255 with df 1 and Asymp. and Sig. (2-sided) value was 0.039 with point of probability 0.018.

4. Discussion

Diabetes mellitus is a group of metabolic disorders accompanied by chronic hyperglycemia due to absolute or relative deficiency of insulin either due to secretion or action leading to disturbances in carbohydrate, protein, and fat metabolism. Diabetes mellitus is the major health problem of the 21st century. Rapid increase in number of diabetics has made the World Health Organization to declare India as the global capital of diabetes. Diabetes mellitus is increasing faster in Asian countries than in other regions. In Asia continent there are >60 percent of diabetics resident on globe. This study yields multiple important

Table 2. Cross tabulation: Gender*DM Groups with and without HTN*Magnesium n = 245.

Magnesium				Group		Total	Chi-square
				Group 1 with HTN.	Group 2 without HTN		Asymp. Sig. (2-sided) p-value
1.5 - 2.5 meq/dl Normomagnesemia	sex	male	Count	39	40	79	<0.951
			% within sex	49.4%	50.6%	100.0%	
			% within hypertension	66.1%	65.6%	65.8%	
			% of Total	32.5%	33.3%	65.8%	
		female	Count	20	21	41	
			% within sex	48.8%	51.2%	100.0%	
			% within hypertension	33.9%	34.4%	34.2%	
			% of Total	16.7%	17.5%	34.2%	
		Total	Count	59	61	120	
			% within sex	49.2%	50.8%	100.0%	
			% within hypertension	100.0%	100.0%	100.0%	
			% of Total	49.2%	50.8%	100.0%	
<1.5 meq/dl Hypomagnesaemia	sex	male	Count	47	34	81	<0.038
			% within sex	58.0%	42.0%	100.0%	
			% within hypertension	73.4%	55.7%	64.8%	
			% of Total	37.6%	27.2%	64.8%	
		female	Count	17	27	44	
			% within sex	38.6%	61.4%	100.0%	
			% within hypertension	26.6%	44.3%	35.2%	
			% of Total	13.6%	21.6%	35.2%	
		Total	Count	64	61	125	
			% within sex	51.2%	48.8%	100.0%	
			% within hypertension	100.0%	100.0%	100.0%	
			% of Total	51.2%	48.8%	100.0%	

demographic variables that are directly or indirectly related to the serum magnesium levels and also with diabetes and hypertension. Low income, lack of education especially health education, unemployment (only 15.6% n = 245 were office workers) and others, these factors contribute to the nutritional deficiency and ultimately hypomagnesaemia and this could be the reason for speedy rise in diabetes and hypertension. An increased prevalence of impaired fasting glucose

was seen since 2000, more among the younger population <50 years of age. This is also an indicator of further increase in prevalence of diabetes, with a risk of approximately 50% conversion to diabetes over 10 years. The important risk factors for diabetes are urbanization, a racial predisposition, genetic risk, aging, obesity, and insulin resistance [19].

The mean age (57.02 + 6.32) of study subjects were more or less comparable with other available studies. Increasing life expectancy, urbanization with life style changes, overweight and obesity were also noted in current study. Also the genetic risk (positive family history of diabetes was found in 39.2%) was an important aspect of current study.

Magnesium is distributed into all three compartments of the body. Nearly 65% of magnesium is present in bones, 34% is found inside the cells and only 1% is present in the extracellular fluid. Magnesium plays fundamental role in cellular metabolic reactions such as protein and DNA production, hormone receptor connecting and neurotransmission. Magnesium is part of GTPase and as a co-factor to Na+/K + ATPase, adenylate-cyclase and phospho-fructo-kinase. A large number of biochemical reactions as well as carbohydrate metabolism depend on magnesium, also insulin secretion and actions are influenced by it [20] [21] [22]. Deficiency of magnesium leads to disturbances in metabolism of glucose and at various levels of insulin secretion and its function in carbohydrate metabolism [23]. Action of insulin, glucose uptake and tone of vessels all are mostly maintained by intracellular magnesium [24].

4.1. Magnesium and Diabetes

Prevalence of Hypomagnesemia among diabetes (Type 2) is reported from 13.5% to 47.7%. Hypomagnesemia had been linked to the reduced control of glycemia thus leading to the macro and microvascular complications of diabetes (coronary artery disease, hypertension, retinopathy, nephropathy, neuropathy and foot ulcers) had been linked with hypomagnesemia. There are multiple factors responsible for high rates of hypomagnesemia in subjects with diabetes (Type 2) [25].

In ARIC (Atherosclerosis risk in Communities) study inverse relationship among serum magnesium levels and coronary artery risk in middle aged diabetic subjects were observed [26].

Resnick *et al.* in their study conducted in subjects with normotensive without diabetes, and hypertensive with and without diabetes concluded that mean intracellular magnesium levels were lowest in subjects who were diabetics with hypertension [27]. A considerable data reported that different micro and macrovascular complications of diabetes were linked with hypomagnesemia.

Decreased levels of magnesium are usually observed in diabetic subjects [28] [29]. Mean serum magnesium values were low in diabetic subjects in comparison with normal controls as measured on spectrophotometery (atomic absorption) by Mather *et al.* [30]. Serum magnesium values were directly associated with serum albumin concentrations and inverse to metabolic control in diabetic

patients. It was established in reports about the increased occurrence of hypomagnesaemia in non insulin dependent DM [31] [32].

4.2. Magnesium and Hypertension

Hypomagnesemia was present in 51.2% of the current study subjects with T2DM (hypertension and without hypertension), Phuong-Chi T. Pham *et al.* had also reported in their study decreased levels of magnesium in diabetic subjects as compared with controls. Basic tone of the blood vessels had directly been modified by magnesium ions [33] [34] [35].

In vitro when magnesium ions were removed from medium leaded to contractions in the arterial muscle [36]. Many irregularities of metabolism of magnesium were observed in hypertensive patients. Decreased levels of Magnesium may be pertinent with hypertension but clinically there is slight confirmation for this. As reported in many epidemiological researches about inverse association amongst magnesium intake and raised blood pressure, decreased nutritional intake of magnesium is related with hypertension [37] [38].

Decreased levels of free intracellular magnesium are general characteristics of diabetes mellitus and hypertension. Reduction in magnesium concentration may lead to insulin resistance, hyper-insulinaemia and may result in raised blood pressure due to vasoconstriction [39].

Present study included 123 (n = 245) hypertensive subjects, hypomagnesemia observed in 52.04% (n = 123) of subjects with hypertension and normomagnesemia was present in 47.96% (n = 123) diabetic subjects with hypertension.

Low serum magnesium levels had been detected in different states like hypertension, ischemic heart diseases, abnormal lipid profiles etc [40] [41].

Magnesium and serum potassium may be involved in development of hypertension; low serum magnesium causes atherosclerosis by different patho-physiological mechanisms [42].

Low serum magnesium may lead to abnormal increased cellular proliferation and increased thickness of arterial wall leading to rise in blood pressure [43].

Patients who were suffering from high blood pressures, ischemic heart diseases and addiction to alcohol, studies had observed that low serum magnesium along with other abnormal levels of electrolytes was seen in them [44].

In the view of above facts it is clear that low serum magnesium is a common problem in diabetics. It affects the diabetes and may lead to development of hypertension, the findings of current study are in match with other studies internationally and serum magnesium should be a routine part of investigation pool of diabetics.

5. Strengths and Limitations

This was a small sample size study, in a local area, with bias but this study was an important opening of research on magnesium and its effects in diabetes with different complications in our setup. No study was conducted yet on magnesium in diabetes with hypertension in our setup; this study will guide the impact of

magnesium on diabetes and to prevent the complication like hypertension by giving magnesium as drug or in food supplements.

6. Recommendations

A multicenter research shall be carried out to observe the magnesium effects on diabetes with and without complications. All patients with diabetes should be investigated for serum magnesium level, if deficient should be corrected on priority basis. Hypomagnesaemia should be corrected on priority basis because studies show that it affects the prognosis and outcome of diabetes.

7. Conclusion

It has been concluded from present research that Hypomagnesaemia is common in type 2 diabetes mellitus with and without hypertension. In the guidance of current results and discussion, T2DM subjects with and without Hypertension may benefit from extra supplementation of magnesium for prevention and as a part of treatment.

Authors' Contributions

Anwar Ali Jamali designed the study protocol, planned analyses, and manuscript draft. Ghulam Mustafa Jamali had done statistical analyses and data interpretation and drafting. Other authors reviewed manuscript draft, critically, contributed to analysis, discussion and interpretation of the data, with writing of the manuscript to data collection.

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Conflict of Interest

No conflict of interest is declared by the authors.

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