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Research Article

Link between distal sensory polyneuropathy, insulin-like growth factor-I and bone mineral density in elderly diabetics

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ABSTRACT

Background: The association between Distal Sensory Polyneuropathy (DSP) and systemic osteopenia was studied before in type 1 Diabetes Mellitus (DM), however, is not all clear, with scanty researches in type 2 DM. In addition, Insulin-like Growth Factor-I (IGF-1) could be the most important mediator of bone growth, and an important neurotrophic factor for peripheral sensory neurons. Therefore, the aim of this study was to study the association between bone mineral density (BMD) and DSP, in elderly patients with type 2 DM, and the link between IGF-1 and both BMD and DSP.
Methods: Eighty eight elderly patients, aged ≥60 years, were involved in this case (43 diabetics with DSP and 17 diabetics without DSP) - control (28 non diabetics) study. BMD and IGF-1 were measured.
Results: There was no significant difference between cases and controls regarding T score of either lumbar spine or femoral neck or IGF-1 (P = 0.83, 0.96 and 0.17 consecutively). DM without DSP had higher IGF-1 than both DM with DSP& the control group (P = 0.011 and 0.010 consecutively). IGF-1 was a significant predictor of T score of both femoral neck and lumbar spine, only in the control group (P = 0.008 and <0.001 consecutively) (OR=1.44 and 2.4 consecutively) (CI=1.1-1.9 and 1.9-3.1 consecutively). Neither DSP nor IGF-1 was (were) a significant predictor of BMD in diabetics.
Conclusion: There was no association between type 2 DM and BMD. IGF-1 was higher in diabetics without DSP than those with DSP or the control group. IGF-1 was a positive predictor of BMD only in the control group.

Keywords: Type 2 diabetes mellitus, Bone mineral density, Sensory neuropathy, IGF-1

INTRODUCTION

Distal Sensory Polyneuropathy (DSP) is the most common type of neuropathy in diabetic patients.[1] Distal polyneuropathy typically presents primarily with sensory deficit, with symptoms starting in the feet, with gradual spreading upwards, eliciting the classic "stocking-glove distribution".[2]

Systemic Insulin-like Growth Factor-I (IGF-1) is synthesized basically in the liver, its synthesis is growth hormone dependent; IGF-1 is additionally produced in multiple extrahepatic tissues, where it acts locally as a growth factor, where is controlled by multiple hormones.[3]

Like nerve growth factor, IGF-I underlies neurotrophic effects in many neurons including peripheral sensory neurons.[4]

In addition, IGF-1 could be the most important mediator of bone growth.[5]

Bone remodeling regulation is mediated by systemic hormones and local factors in order to maintain bone mass. IGF-1 is an important anabolic regulator of bone cell function, as decreasing collagen degradation, enhancing bone matrix deposition, and increasing recruitment of osteoblastic cells.[6,7]

The association between DSP and systemic osteopenia, was studied before in type 1 diabetes mellitus (DM), however, is not all clear. Forst et al. reported decreased bone mineral density (BMD) of the femoral neck, but not in other skeletal sites in diabetic patients with DSP,[8] and Rix et al. reported possible systemic osteopenia in patients with type 1 DM and DSP.[9]

However, to our knowledge, the link between BMD and DSP was not discussed before in type 2 DM.

Therefore, the aim of this study was to study the association between systemic BMD and DSP, in elderly patients with type 2 DM, and the link between IGF-1 level and both BMD and DSP.

METHODS

Eighty eight elderly patients, aged ≥60 years, were involved in this case control study. The cases were divided into 2 groups: group 1 consisted of 43 patients with DM and DSP and group 2 consisted of 17 patients with DM without DSP, the control group consisted of 28 subjects without DM [fasting blood sugar (FBS) <100 mg/ dl in the absence of antidiabetic treatment and symptoms], based upon the recommendation of FBS as screening method due to reproducibility, sensitivity and correlation with microangiopathic complications.[10] The patients were recruited from the geriatric outpatient clinic in Ain Shams University Hospital. An informed consent was taken from all participants and the study was approved by the ethical committee of the faculty of medicine, Ain Shams University.

Diagnosis of DM was based upon American diabetic association criteria in 2013.[11]

Positive history of other microangiopathies, nephropathy or retinopathy, was reported.

Positive screening for DSP was done based upon positive result(s) of either the Diabetic neuropathy symptom score, suggested as an enough sensitive screening method alone,[12] and/or positive pinpricking test, as it tests small fiber involvement,[13] which is known to be involved at first in diabetic neuropathy.[14] A toothpick was used and the peripheral sensation was tested in reference to that on the sternum from a distal to proximal approach.

Basic activities of daily living (ADL) assess the ability of the patient to complete basic self-care tasks. ADL were scored in the following manner; low ADL = dependent in 0-3 key ADL, medium ADL = dependent in 4-6 key ADLs, and high ADL = dependent in 7-8 key ADL.[15]

Assessment of BMD by dual energy x-ray absorptiometry (DEXA), in the osteoporosis unit in the geriatrics and gerontology department in Ain Shams University using DPX-L densitometer (Lunar) instrument, was done in two sites; femoral neck and lumbar spine. T score was calculated for both sites.

Serum level of IGF-1 was measured in all participants. Venous blood samples were collected, centrifuged and stored at -70°C till being assayed. IGF-1 was measured by Enzyme-Linked Immunosorbent Assay (ELISA) using kits supplied by DRG (DRG international, New Jersey, USA).

Exclusion criteria: Patients with history of alcoholism, hypothyroidism, acromegaly,[16] or causes for secondary osteoporosis (except DM) were excluded according to the history and appropriate investigations.

Data analyses were performed using the 16thversion of SPSS. Qualitative data were presented in frequency tables. Normality distribution of the variables was tested using one sample Kolmogorov Smirnov test. Quantitative data were presented in the form of mean ± SD for parametric data, and median and rank values for non-parametric data. P value was set at 0.05. To compare quantitative data between 2 groups, Two independent t-test was used for parametric data and Mann-Whitney U test was used for non-parametric data. To compare quantitative data between 3 groups, Analysis of variance (ANOVA) was used for parametric data, and Kruskal-Wallis H was used for non-parametric data. Chi square or Fisher's Exact test was used to compare qualitative data. Pearson correlation was used for correlation between quantitative variables.

Linear logistic regression analysis was used to detect if IGF-1 level could have impact upon femoral neck or lumbar spine T score, in elderly within each group and further impact of DSP in group 1 with and without adjustment for other micro-vascular complications.

RESULTS

Eighty eight elderly patients, aged ≥60 years, were studied. Their age median was 63, and 50% were males.

There was no significant difference between cases and controls regarding age or smoking index (P = 0.09 and 0.83 consecutively) (Table 1).

There was no significant difference between cases and controls regarding T score of lumbar spine, T score of femoral neck or IGF-1 (P = 0.83, 0.96 and 0.17 consecutively) (Table 2).

Table 1: Comparing between diabetics and non-diabetics regarding demographic and clinical data.

Variables	Cases (with DM) n=60	Control group n=28	P value
Age (years)	63 (41.5)	66 (50)	0.09
Gender (male)	30 (50%)	14 (50%)	1
Ex-smoker	0 (0%)	7 (11.7%)	0.13
Current smoking	9 (32.1%)	13 (21.7%)	
Smoking index (pack-years)	0 (44.8)	0 (43.8)	0.83
low trauma fracture	4 (6.7%)	0 (0%)	0.3
Body mass index	33.5 ± 8.9	29.9 ± 6.9	0.06
ADL	2 (3.3%)	0 (0%)	0.13

Quantitative data were presented in the form of mean ± SD for parametric data, and median (rank) values for non-parametric data. Qualitative data were expressed in the form of number and frequency.

ADL: Basic activities of daily living, DM: diabetes mellitus

Table 2: Comparing between diabetics and non-diabetics regarding BMD and laboratory data.

Variables	Cases (with DM) n=60	Control group n=28	P value
T score of lumbar spine	-1.53 ± 1.6	-1.44 ± 2.1	0.83
T score of femoral neck	-1.32 ± 1.22	-1.31 ± 1.38	0.96
IGF-1(ng/ml)	4.65 ± 2.2	4.12 ± 1.4	0.17

Quantitative data were presented in the form of mean ± SD

DM: diabetes mellitus, IGF-1: Insulin-like growth factor-I

There was significant difference between the 3 groups in IGF-1 level (P = 0.02) (Table 3).

By post hoc analysis, using Lease Significant Difference (LSD), DM without DSP had higher IGF-1 level than both DM with DSP& the control group (P = 0.011 and 0.010 consecutively) (Table 4).

Table 3: Comparing between the 3 groups regarding demographic, clinical, radiological and laboratory data.

Variables	DM with DSP n=43 (48.9%)	DM without DSP n=17 (19.3%)	Control group n=28 (31.8%)	P value
Age (years)	63 (40.4)	62 (44.3)	66 (50.9)	0.22
Gender (male)	19 (44.2%)	11 (64.7%)	14 (50%)	0.36
Ex-smoker	3 (7%)	4 (23.5%)	0 (0%)	0.06
Current smoking	11 (25.6%)	2 (11.8%)	9 (32.1%)	
smoking index (pack-years)	0 (45.4)	0 (43.4)	0 (43.8)	0.92
low trauma fracture	4 (9.3%)	0 (0%)	0 (0%)	0.11
Retinopathy	13 (30.2%)	0 (0%)	0 (0%)	<0.001
Nephropathy	8 (18.6%)	0 (0%)	0 (0%)	<0.001
Body mass index	34.36 ± 9.3	31.32 ± 7.5	29.87 ± 6.9	0.08
ADL (dependent)	2 (4.7%)	0 (0%)	0 (0%)	0.09
T score of lumbar spine	-1.49 ± 1.6	-1.61 ± 1.6	-1.44 ± 2.1	0.95
T score of femoral neck	-1.23 ± 1.2	-1.55 ± 1.2	-1.30 ± 1.4	0.68
IGF-1(ng/ml)	4.25 ± 2.1	5.67 ± 2.2	4.12 ± 1.4	0.02

Quantitative data were presented in the form of mean ± SD for parametric data, and median (rank) values for non-parametric data. Qualitative data were expressed in the form of number and frequency.
ADL: Basic activities of daily living, DM: diabetes mellitus, DSP: Distal sensory polyneuropathy, IGF-1: Insulin-like growth factor-I

Table 4: Post hoc analysis of IGF-1.

Group type	Mean difference	P	95% confidence interval
DM with/without DSP	1.43	0.011	0.34- 2.5
No DM	1.56	0.010	0.39- 2.7

DM: diabetes mellitus, DSP: Distal sensory polyneuropathy

There was no significant difference between group 1 and 2 in DM duration (P = 0.62). Using Pearson correlation, IGF-1 level was significantly correlated with T score of both femoral neck and lumbar spine, only in the control group (P = 0.05 and 0.001 consecutively) (r = 0.37 and 0.6 consecutively) (data were not presented in table).

Using logistic regression, IGF-1 level was a significant predictor of T score of both femoral neck and lumbar spine, only in the control group (P = 0.008 and <0.001 consecutively) (OR=1.44 and 2.4 consecutively) (CI=1.1-

1.9 and 1.9-3.1 consecutively). Neither DSP nor IGF-1 level was a significant predictor of BMD in group 1 either alone, together or with additional adjustment for nephropathy and retinopathy (Table 5).

Table 5: Logistic regression test for predictors of T score of both femoral neck and lumbar spine.

	Femoral neck			Lumbar spine		
Variables in regression	**P value**	**Odd ratio**	**Confidence interval (95%)**	**P value**	**Odd ratio**	**Confidence interval (95%)**
Diabetics with DSP						
IGF-1	0.92	1.01	0.14-0.56	0.57	0.958	0.83-1.11
IGF-1*	0.86	0.99	0.85-1.14	0.57	0.958	0.83-1.11
IGF-1**	0.92	1.00	0.87-1.17	0.64	1.1	0.51-2.4
Diabetics without DSP						
IGF-1	0.093	0.827	0.662-1.032	0.188	0.862	0.690-1.076
Control group						
IGF-1	0.008	1.44	1.1-1.9	<0.001	2.4	1.9-3.1

*With adjustment for DSP
** With adjustment for DSP, retinopathy, nephropathy
DSP: Distal sensory polyneuropathy, IGF-1: Insulin-like growth factor-I

DISCUSSION

In the current study, DM without DSP had significantly higher IGF-1 level than the control group. This could be explained by the consequences of increased insulin/IGF-1 signaling, mediated in part by hyperglycemia and hyperglycemic diet, upon inadequate elimination of reactive oxygen species (ROS), a critical mechanism involved in the promotion of type 2 DM.[17] In addition, glucose is implicated in inducing β-cells to secrete insulin and IGF-1. However, islet β-cell dysfunction also occurs from the oxidative stress of elevated ROS levels.[17]

This is in accordance with Janssen and Lamberts hypothesis of the impact of the progressive decline in IGF-I in elderly diabetics that ultimately results in losing its protective effects upon the kidneys, eyes and neurons, and followed by the progression of diabetic microvascular complications.[18] In addition, the link between low IGF-1 and microangiopathy in general, is further proved by the link between retinopathy with low IGF-1.[19] Therefore, it is suspected that early stage of type 2 DM, uncomplicated, is associated with increased IGF-1 level, while it is decreased with further disease progression, with excess ROS, leading to complication as DSP.

This supports our finding of lower IGF-1 level in diabetic patients with DSP rather than those without, which is in accordance with Migdalis et al. who found lower levels IGF-1 in patients with type 2 DM with DSP rather than those with DM without DSP, and additionally suggested possible IGF-1 receptor abnormality in the neuropathic group.[20]

The possible IGF-1 receptor abnormality in type 2 DM with DSP,[20] plus the link between ROS and DSP,[21] might explain the current findings of the presence of DM complicated with DSP, along with the insignificant difference between the neuropathic and control groups in IGF-1.

Although, some authors found that the control group had higher level of IGF-1 than the neuropathic diabetic group,[22] this difference with our results could be linked to their use of Dyck criteria for diagnosis of peripheral neuropathy, which depend on the presence of 2 abnormalities in their tests, from which is nerve conduction that fails to detect lesion in small fibers.[13] Therefore, there sample possibly had more severe forms of DSP than ours and consequently lower IGF-1 level than controls.

Current study demonstrated that higher IGF-1 level is a predictor of better BMD, only in non-diabetics. The positive effect of IGF-1 in non-diabetics is supported by its usage as treatment. It has been reported that, independent of age, IGF-1 treatment is effective in enhancing gene expression of osteoblastic markers, suggesting exogenous IGF-1 as a potential treatment in age-related bone loss.[23] On the other hand, IGF-I receptors expression has also been found in mature rabbit osteoclasts, and in human pre-osteoclasts,[24] and IGF-I induces the formation of osteoclast-like cells in bone marrow cultures.[25]

This controversy could be explained by Grinspoon et al. who reported that with high doses, IGF-I increases bone remodeling, however at low doses it enhances bone formation without an effect on bone resorption.[26]

We did not report a positive effect for IGF-1 upon BMD in group 2 diabetics, in the presence of higher IGF-1 level in diabetics without DSP, or group 1 diabetics. This may be attributed in part to their action on insulin receptors, as IGF-1 binds weakly to the insulin receptor,[27] In a mice model, it was found that defective both insulin receptors and IGF-1 receptors , rather than insulin receptors only, is a cause for type 2 DM.[28]

Furthermore, although the GH/IGF-1 provides the main stimulus for bone growth regulation through activating the osteoblast differentiation program,[29] the factors associated with the diabetes, as insulin resistance and hyperglycemia, in the type 2 diabetic mice model may cause a shift in the marrow osteoclast precursor pool and its sensitivity to osteoclast regulatory factors. Despite a scanty of data, there has been a wide acceptance of the idea that increased activity by osteoclasts does not have a role in type 2 DM-related bone disease due to low bone turnover.[30] These can explain the absence of negative or positive association between IGF-1 level and BMD, in diabetics, and further support the current data regarding the absence of significant association between DM and BMD. Although, There is a lack of data on osteoporosis in patients with type 2 DM,[31] with controversies between results regarding bone density as unchanged, increased,[32,33] or decreased.[34] These controversies better to be solved by the histological data from transiliac bone biopsies from 6 subjects with type 2 DM by Krakauer et al. who demonstrated low bone turnover, hypothesizing a protective effect of the low bone turnover state over time in aging with type 2 DM.[35]

The current work reported no significant association between DSP and BMD. This is in accordance with Amir et al. who reported no correlation between microangiopathy and histomorphometric changes in bone.[36]

On the other hand, others found association between DSP, even after control of other microangiopathic complication, and generalized decrease in BMD.[9] They attributed this to the hypothesis of that neuropathy and /or microangiopathy leads to the opening of arteriovenous shunts, and the resultant increase in venous pressure may lead to increased osteoclastic activity and therefore demineralization of bone.[37,38]

On the contrary, the relationship between bone remodeling and increased intraosseous pressure was studied in the vertebrae of the rat tail. They found that prolonged venous hypertension resulted in increased osteoblastic activity with new bone formation.[39]

A shortcoming of the current study was the absence of grading for DSP. Therefore, comparison between different grades of DSP and IGF-1 level might be suggested for future researches.

CONCLUSION

There was no association between type 2 DM and BMD. IGF-1 level was higher in diabetics without DSP than those with DSP or the control group. IGF-1 level was a positive predictor of BMD only in the control group.

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