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Increased serum pentosidine level is a predictor for severe knee osteoarthritis in diabetic type 2 patients

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Abstract : The term Diabetes Mellitus, describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both. It has been suggested that type 2 diabetes is important risk factor for development of osteoarthritis. Diabetes affects cartilage metabolism and osteophyte formation of knee joint. Pentosidine, one of advanced glycation end products; it contributes to the pathogenesis of osteoarthritis. It is found to be raised in patients with Diabetes Mellitus. This paper gives summary of deleterious effect of diabetes mellitus on knee osteoarthritis.
Keywords: Diabetes Mellitus**,** osteoarthritis, pentosidine**,** advanced glycation end products**,** chronic hyperglycemia**,** knee joint.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disease of high morbidity and mortality,(1) The effects of diabetes include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels. (2) The incidence of DM and the life expectancy of diabetic patients have both increased, resulting in an elevation in the prevalence and clinical importance of those osteomuscular changes. The following have been described in diabetic patients: stiff hand syndrome, Dupuytren's contracture, trigger finger; shoulder capsulitis, calcific periarthritis of the shoulder, carpal tunnel syndrome, muscular infarction, diffuse idiopathic skeletal hyperostosis (DISH) and Charcot's arthropathy.(3, 4) In addition, a higher prevalence of crystal arthritis, infections, osteoporosis and osteoarthritis has been reported.(5)

Hyperglycemia is also known to favor the production of advanced glycation end product (AGEs) and their accumulation in articular cartilage, which contribute to a toxic environment that might facilitate OA pathogenesis.(6)

The accumulation of AGEs cross-links in collagen adversely affects the mechanical properties of connective tissues like articular cartilage.(7, 8) The increase in stiffness is highly correlated with collagen AGEs levels.(8) Advanced glycation end products interfere with cartilage metabolism. The age-related decrease in matrix synthesis by articular chondrocytes(9, 10) is largely explained by the impaired synthesis of collagen(11) and proteoglycansat high cartilage AGE levels. (9)

There is a little information about body fluid levels of pentosidine and its consequences in OA.(12) DeGroot(13) detected higher urine pentosidine levels in patients with OA than in controls and calculated a

predictive quotient using pentosidine to determine the presence of OA. Moreover, Senolt L[14] documented an increase in the pentosidine concentration in serum from patients with OA, with pentosidine being a predictive marker of further disease progression.

Thus we aim to study prevalence and severity of knee OA among diabetic patients and measure serum pentosidine level and correlation to severity of diabetic knee OA.

1. Methods

Subjects

The study included: One hundred type 2 diabetic patients selected from Diabetes Clinic and Physical Medicine, Rheumatology and Rehabilitation Clinic of The Main University Hospital. In addition one hundred age and sex matched non-diabetic subjects will constitute the control group. The diabetic patients were inquired about having knee pain. Seventy six of those patients stated having knee pain and were diagnosed knee OA by fulfilling ACR criteria. [15] Participants who have renal disease were excluded. The non-diabetic persons all attending the clinic for purposes not relevant to knee complains were also inquired about having knee pain. Knee OA was diagnosed in those patients with positive knee pain who fulfilled ACR criteria. The subjects were inquired about history of knee pain and were clinically examined for signs of knee OA.

The following data were be recorded for each case:

History and Demographic data: Name, age, sex, occupation, disease duration, height, weight and BMI.

Clinical: Complete clinical examination of the knee joint was done to detect the following: Alignment, swelling, tenderness by Ritchie Articular Index,[16] effusion, crepitus, stability, range of motion in degrees, muscle power of muscles around the knee was tested using the Medical Research Council (MRC) grades,[17] quadriceps wasting (thigh girth), abnormal gait. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[18,19] was included for evaluation of patient activities and participation

Radiological: Radiographic abnormality of the knee joint was assessed using plain X-Ray of both knees antero-posterior and lateral views while standing and the disease severity was assessed by using the Kellgren and Lawrence global scale. [20]

Laboratory methods including: Serum pentosidine and Hb A1c levels were measured in subset of knee OA patients among diabetic patients and control group. [21]

2. Statistical analysis

After collection of data, it was coded and transformed into a specially designed format to be suitable for computer feeding. All entered data were verified for error. Data were analyzed using the Statistical Package for Social Sciences (SPSS ver.20 Chicago, IL, USA). The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, which revealed that the data normally distributed. Quantitative data were described using mean, standard deviation. Qualitative data were described using number and percent. Correlation between quantitative variables and score variables was done using Pearson product-moment correlation coefficient. Comparing quantitative variables between 2 groups was conducted using independent sample t-test. Chi square test used to test association between 2 qualitative variables and Monte Carlo significance test (MCP) used (if more than 20% of cells have expected cell count <5) in more than (2x2). In all statistical tests, level of significance below which the results were considered to be statistically significant is 0.05.

3. Results

The mean value of Hb A1C among the studied diabetic patients was 7.21%±0.96. Considering a cutoff point Hb A1C,[22] 36.84% of the studied diabetic patients are considered controlled diabetics while 63.15% were not controlled.

Table (1): Serum pentosidine level among patient of the studied groups.

	Diabetic OA (n = 45)	**Non Diabetic OA (n = 30)**	**Total (n = 75)**
Serum pentosidine level (nmol/ l)			
Min. – Max.	6.0 – 150.0	5.0 – 65.0	5.0 – 150.0
Mean ± SD	34.79±32.23	23.12±12.69	30.12 ± 26.72
t(p)	2.05* (0.043*)		

t: Student t-test

*: Statistically significant at $p \leq 0.05$

Table (1) shows descriptive statistics of serum pentosidine level among diabetic and non-diabetic groups of knee OA. There was statistically significant difference between mean values pentosidine serum level of the two studied groups. Serum pentosidine level has been found to be significant higher among diabetic than non-diabetic knee OA patients (34.79 nmol/l ±32.225, t=2.05, P=0.043).

Table (2): Correlations between serum pentosidine level with disease duration of OA and DM as well as with glycated Hb in the diabetic group of knee OA.

		Pentosidine level	**Duration of OA**	**Duration of DM**
Duration of OA	**r**	0.851*		
	p	0.0001*		
Duration of DM	**r**	0.952*	0.971*	
	p	0.0001*	<0.001*	
HbA1 c	**r**	0.957*	0.667*	0.636*
	p	0.0001	0.0001*	0.0001*

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

Table (2) shows correlation between serum pentosidine level with disease duration of OA and DM as well as with glycated Hb in patients of the diabetic group of knee OA. Highly significant positive correlation has been found between serum pentosidine level and the other variables. The longer the duration of DM and OA, the higher the serum pentosidine level. The less the control of DM the higher the serum pentosidine level.

In addition, table (2) showed significant positive correlation between duration of diabetic illness and duration of knee OA. Finally, Hb A1c as a measure of diabetic control showed positive correlation with duration of DM and duration of knee OA.

Table (3) Serum Pentosidine level and Hb A1 C in diabetic OA group regarding Kellgren- Lawrence grading of knee OA:

	Kellgren-Lawrence grading of knee OA				**F**	**p**
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**		
Pentosidine level (N=45)	**(n=7)**	**(n=21)**	**(n=11)**	**(n=6)**		
Min. – Max.	6.0 – 14.0	8.0 – 40.0	14.0 – 80.0	65.0 – 150.0	10.25*	0.001*
Mean ± SD	9.86 ± 3.70	16.88 ± 7.80	52.45 ± 18.16	94.17 ± 32.93		
LSD	All gps. Sig.					
Hb A1 c (N=76)	**(n=7)**	**(n=30)**	**(n=25)**	**(n=14)**		
Min. – Max.	6.0 – 6.0	6.0 – 8.0	6.0 – 9.0	7.0 – 10.0	6.05*	0.032*
Mean ± SD	6.21 ± 0.12	6.59 ± 0.65	7.70 ± 0.69	8.18 ± 0.78		
LSD	I , II # III, VI					

F: F test (ANOVA)

*: Statistically significant at $p \leq 0.05$

LSD: least significant difference.

Table (3) shows comparison between patients with different grading of knee OA according to Kellgren-Lawrence grading of knee OA in the diabetic group of knee OA. Serum pentosidine was significantly higher in patients with grade 3 and 4 of knee OA than in patient with grade 1 and 2 of knee OA ($\overline{X}$ 52.45 ± 18.16, $\overline{X}$ 94.17 ± 32.93, $\overline{X}$ 9.86 ± 3.70, $\overline{X}$ 16.88 ± 7.80, respectively. F=10.25, p =0.001). Hb A1C was significantly higher in patients with grade 3 and grade 4 of knee OA in comparison to grade 1 and 2 of knee OA ($\overline{X}$ 7.70 ± 0.69, $\overline{X}$ 8.18 ± 0.78, $\overline{X}$ 6.21 ± 0.12, $\overline{X}$ 6.59 ± 0.65, respectively, F=6.05, p=0.032).

4. Discussion

Collectively, the results of radiological scoring reflect increased severity of knee OA among diabetic knee OA patients compared to non-diabetics. The specific observation of decreased osteophyte score among diabetics can be explained in light of the pathophysiologic effects of type 2 DM.

The observed increased narrowing of joint space among diabetic knee OA patients can be explained in the view of the diabetes-relevant increased activity of pro-inflammatory cytokines incriminated in increased rates of cartilage destruction. [23, 24]

In agreement with the present study Hussien in 2013[25] found that there was a significant difference; regarding knee joint space narrowing grading i.e. occurrence of grade 1 knee joint space narrowing was higher in diabetic group than non-diabetic one, while grade 2 and grade 3 knee joint space narrowing were noted to occur only in diabetic group. This study also revealed that diabetic group patients have high numbers of subchondral sclerosis than non-diabetic one.

Eymard et al in 2015[26] found that type 2 DM was a predictor of radiologic joint space reduction in men with established knee OA.

Schett et al in 2013[27] also found that type 2 diabetes is a strong predictor for the development of clinical and radiologic severe OA. This finding is independent of age and BMI and suggests that longstanding diabetes per se is detrimental for knee and hip joints, leading to progressive destruction and joint failure. Also, they stated that arthroplasties due to severe symptomatic hip/ knee OA were performed in diabetic subjects.

Serum pentosidine level was significantly higher among diabetic than non-diabetic OA patients. The increased level of serum pentosidine in diabetic knee OA compared to non-diabetics may justify the assuming of the contribution of high serum pentosidine level to the more severe expression of OA among the studied type 2 diabetics. This was further established by finding positive correlation between pentosidine and variable indicators of severity of knee OA among the studied diabetic knee OA group.

Hyperglycemia-induced formation of AGEs is related to diabetic neuropathy; AGE-modified peripheral nerve myelin is susceptible to phagocytosis by macrophages and contributes to segmental demyelination; modification of major axonal cytoskeletal proteins such as tubulin, neurofilament, and actin by AGEs results in axonal atrophy, degeneration and impaired axonal transport; and glycation of extracellular matrix protein laminin leads to impaired regenerative activity in diabetic neuropathy.[28]

Advanced glycation end products in general and pentosidine in particular have been implicated in pathogenesis of OA irrespectively to diabetes through several mechanisms: Accumulation of AGE cross-links in collagen and cause stiffness of the collagen network.[7, 8] Also, AGEs interfere with cartilage metabolism. Through impairment of synthesis of collagen[11] and proteoglycans.[9] Accumulation of AGEs also directly affects matrix turnover by changing the physical and chemical properties of matrix proteins resulting in chondrolysis.[11, 29]Accumulation of AGEs in extracellular matrix proteins may also interfere with chondrocyte-matrix interactions.[30] It was suggested that formation of AGEs in intracellular enzymes and proteins may contribute to impaired cell functioning.[31, 32] AGEs increase pro inflammatory cytokines as IL-6, IL-8 and TNF-α.[33]

Senolt L et al in 2005[12] found that significantly increased serum pentosidine level was detected in patients with OA compared to control group. In fact, increased serum pentosidine concentration in patients with OA and its correlation with the cartilage destruction marker COMP in synovial fluid suggests that pentosidine

may be important in OA pathology and is a new potential OA marker. Verzijl et al[34] in 2001 found that increasing cartilage AGE resulted in increased stiffness of the collagen network. Chiba et al in 2015[35] found that serum pentosidine concentration was significantly correlated with the length of osteophyte in the knee osteoarthritis. AGEs have been considered to be related to the development of vascular endothelial growth factor (VEGF); pro-inflammatory cytokine, by action on specific ligands of cell membrane receptor. Higher pentosidine concentration seems to be one of the risk factors which develop osteophytes in knee osteoarthritis by affecting the increase of VEGF or cytokine.[36, 37]

Based on the present data, the results of the current study appear to establish a cause-effect relationship between serum pentosidine and severity turnover of knee OA among diabetic patients.

5. Conclusion

Diabetes mellitus related factors have been found significantly associated and correlated with the occurrence of moe severe manifestations of knee OA among diabetic patients. These factors included the duration of diabetic illness, control of DM as measured by Hb A1C, and serum pentosidine level.

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7. Abbreviations

DM **Diabetes Mellitus**
OA **Osteoarthritis**
AGEs **Advanced glycation end products.**
DISH **Diffuse idiopathic skeletal hyperostosis**
ACR **American College of Rheumatology**
BMI **Body Mass Index**
MRC **Medical Research Council**
WOMAC **Western Ontario and McMaster Universities Osteoarthritis Index**
Hb A1C **Glycosylated hemoglobin**
IL **Interleukin**
TNF **Tumor necrosis factor**
COMP **Cartilage oligomeric matrix protein**
VEGF **Vascular endothelial growth factor**

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