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1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001; 345:1359-1367.

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Dear Colleague,

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Once again, we hope to meet your expectations, and until we meet in our next issue, deepest regards and best wishes.

The Editor

Prof. Samir Helmy Assaad Khalil

Original Article

Relation of Peak Plantar Pressure to Microvascular Complications in Patients with Type 2 Diabetes

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ABSTRACT:

Background: *The epidemic of diabetes mellitus and its micro vascular and macrovascular complications is a major global health threat. Diabetic Foot Ulcer (DFU) is caused by the interplay of several factors, but most notably diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), and changes in foot structure, resulting in foot deformity and increased weight bearing pressure. The aim of the present study is to study the relation between peak plantar pressure, and diabetic micro vascular complications in patients with type 2 diabetes mellitus.* ***Patients & Methods:*** *This cross sectional study included 64 T2DM subjects with peripheral neuropathy and 64 T2DM subjects without peripheral neuropathy. Data from all subjects were collected and analysed to assess factors affecting diabetic neuropathy and the relation of Peak Plantar Pressure (PPP), using a Presto-scan Tekscan pressure measurement system, with diabetic microvascular complications (retinopathy, nephropathy and neuropathy).* ***Results:*** *Diabetic retinopathy and PPP were higher in the neuropathic group with statistically significant difference between both groups. UACR was high in the neuropathic group but with no statistically significant difference between both groups. There was no significant relation between PPP and diabetic retinopathy or nephropathy.* ***Conclusion:*** *Our data suggest that diabetic retinopathy may be a risk factor for peripheral neuropathy but not a predictor for high PPP. Also, peripheral neuropathy is a predictor of high PPP and hence future foot ulcers. Also, our study suggests that HbA1C, obesity and fissures are factors affecting PPP.*

Keyword: **PPP, DM, Microvascular Complications**.

INTRODUCTION:

The epidemic of diabetes mellitus and its complications poses a major global health threat. The International Diabetes Federation (IDF) estimated that 1 in 11 adults aged 20–79 years (463 million adults) had diabetes mellitus globally in 2019.(1)

Over 90% of diabetes mellitus cases are type 2 diabetes mellitus (T2DM).(2,3) It was estimated that 5.0 million deaths are due to diabetes mellitus and its complications during 2019 in an IDF report, which is equivalent to one death every six seconds.(1)

It is estimated that more than 20 and up to 40% of diabetic patients will develop chronic kidney disease (CKD).(4, 5) CKD can progress to end-stage renal disease (ESRD) requiring dialysis or kidney transplantation and is the leading cause of ESRD in the U.S.(6) Accordingly, the American Diabetes Association (ADA) recommend screening all adults with type 2 diabetes for increased urine albumin excretion when they are first diagnosed with diabetes and at least annually thereafter.(7-9)

Diabetic retinopathy (DR) is a major complication of diabetes mellitus (DM), which remains a leading cause of visual loss in working-age populations, with prevalence

strongly related to both the duration of diabetes and the level of glycemic control.[10] Patients with type 2 diabetes who may have had years of undiagnosed diabetes and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.[11] If diabetic retinopathy is present, prompt referral to an ophthalmologist is recommended.

Peripheral neuropathy is the most common form of neuropathy caused by diabetes. DPN affects the three divisions of the peripheral nervous system; sensory, motor and autonomic.[12] Most common among diabetic neuropathies is chronic DSPN, accounting for about 75% of the diabetic neuropathies.[13,14] All patients with type 2 diabetes should be assessed annually for DPN. Screening should start at time of diagnosis in T2DM and after five years in T1DM. Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain, burning and tingling. The involvement of large fibers may cause numbness and loss of protective sensation (LOPS) which is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation :[15]

- Small-fiber function: pinprick and temperature sensation
- Large-fiber function: vibration perception and 10-g monofilament
- Protective sensation: 10-g monofilament

As in other diabetes-related complications, hyperglycemia appears to be a significant factor in stroke. Hyperglycemia is a significant predictor of fatal and nonfatal stroke,[16] and death from stroke.[17] Cardiovascular disease (CVD) is the leading cause (∼70%) of death in people with type 2 diabetes.[18,19]

Foot ulceration in people with diabetes will continue to be a major public-health concern, considering the 15–25% lifetime risk of developing a foot ulcer.[20,21] At least 15% of these ulcers will lead to some form of foot amputation.[22] DFU is caused by the interplay of several factors, but most notably diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD) and changes in foot structure, resulting in foot deformity and increased weight bearing pressure.[23-25] The plantar pressure pattern and value can be determined by a pedobarographic examination. The pedobarograph is a device which converts the applied pressure into a visible light pattern with a pressure measurement.[26] Recently, the plantar pressure has widely been accepted as a vital biomechanical parameter to evaluate human walking. In population with diabetes, also poor control of the disease seems to be responsible for abnormal foot pressure.[27, 28] The study was designed to assess the relation between peak plantar pressure and the presence of diabetic microvascular complications in patients with type 2 diabetes mellitus.

SUBJECTS:

Study Design: Sixty four patients (21 men and 43 women) aged between 41 years and 73 years with diabetic peripheral neuropathy and sixty four patients (12 men and 52 women) aged between 41 years and 74 years with T2DM but no peripheral neuropathy were enrolled in the current study from among patients attending the outpatient clinics of the Department of Diabetes, Lipidology and Metabolism, Alexandria Main University Hospital. The study design was approved by the Ethics Committee of Alexandria University. The study was conducted according to the criteria set by the Declaration of Helsinki, an informed consent was signed by participants before any study related procedure.

Exclusion Criteria: Patients with age <18 years, those with unsteady gait related to other conditions, nondiabetic kidney disease (other than renal stone), decompensated heart failure, end stage liver disease, chronic inflammatory or autoimmune disease, cancer patient, other metabolic disease, pregnancy and other endocrinal diseases.

METHODS:

All participants underwent the following:

Clinical assessment: Full assessment of history stressing on duration and treatment of diabetes, smoking, hypertension, presence of micro or macrovascular diabetic complications and neurological symptoms. BMI was calculated and BP was measured.

Foot assessment: Skin inspection and musculoskeletal examination for foot deformities and limited joint mobility. Neurological examination including: deep tendon reflexes, vibration perception at great toes using the biothesiometer (Diabetica solutions Inc., USA), and 10g-Semmes-Weinstein Monofilament test (A 5.07 Semmes-Weinstein nylon monofilament was employed to apply a consistent 10 g force on 9 different sites on the plantar surface of the foot for about one second). Peripheral neuropathy was diagnosed if bilateral absence of reflexes either at rest or during reinforcement [(29)], symmetrical abnormality in vibration perception (VPT more than 25 V) [(30)] or symmetrical abnormality in monofilament test (less than 7) [(31)]. ABI was calculated and assessed.

Assessment of mean peak plantar pressure (PPP) on 3 trials of barefoot pressure using 2 step gait initiation protocol on a Presto-scan Tekscan pressure measurement system (Boston, MA, USA).[(32)]

Ophthalmoscopic fundus examination

Laboratory investigations: Blood drawn for metabolic, biochemical and hematological parameters after a 12 hours overnight fasting and estimate the following: complete blood picture, fasting serum glucose, urea, creatinine and eGFR according to CKD EPI-equation, urinary albumin excretion (UAE) and albumin creatinine ratio, Glycated hemoglobin (HbA1C) and Lipid profile (Triglycerides, LDL-c, HDL-c, Total cholesterol).[(33-37)]

Statistical Analysis: Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, and standard deviation, median and interquartile range (IQR). The Student's t-test was used to compare parameters between the two diabetic groups. Mann-Whitney U test was used for abnormally distributed quantitative variables, to compare between two studied groups. The Chi square ($\chi 2$) test was used to compare categorical variables between groups. Fisher's Exact or Monte Carlo correction was used as correction for chi-square when more than 20% of the cells have expected count less than 5. Regression was used to detect the most independent/ affecting factor affecting the peripheral neuropathy and also peak planter pressure. All statistical analyses were carried out using the SPSS software (version 20.0; IBM Corporation, Armonk, NY, USA).

RESULTS: ***Comparison between both groups:*** There was no significant difference in gender, age, BMI, urinary albumin creatinine ratio between the studied groups, but there was statistically significant difference between them as regards smoking history, anti- diabetic medication, duration of diabetes, glycemic profile, DNS score, finding on fundus examination and PPP as these variables were higher in the neuropathic group.

Regression analysis for risk factors of diabetic peripheral neuropathy (Table I): HbA1c, duration of diabetes, smoking history, eGFR, and finding on fundus examination were independently statistically significantly positively affecting neuropathy in the univariate analysis ($p<0.001$), ($p=0.001$), ($p=0.041$), ($p=0.006$), ($p=0.001$) respectively and in the multivariate analysis only HbA1c significantly positively affecting neuropathy ($p<0.001$).

Relations with PPP: There was no statistically significant relation between PPP and diabetic retinopathy, UACR, eGFR, BMI and HbA1C, there was statistically significant relation between PPP and foot fissures in both neuropathic and non-neuropathic groups.

Regression analysis for factors affecting PPP(Table II): Regression analysis for factors affecting PPP for the total sample univariate analysis showed that neuropathy, HbA1c, foot fissures and BMI were independently statistically significantly positively correlated with the PPP ($p=0.001$), ($p=0.005$), ($p=0.001$), ($p=0.036$) respectively and multivariate analysis showed that neuropathy, foot fissures and BMI were statistically significantly

positively correlated with the PPP (p=0.014), (p=0.002), (p=0.035) respectively.

Regarding univariate and multivariate regression analysis for factors affecting PPP in neuropathic group our study showed that BMI and smoking history were independently statistically significantly positively correlated with the PPP (p<0.023), (p=0.031) respectively in the univariate analysis and none of the studied factors was with statistically significant relation with PPP in the multivariate analysis.

In non-neuropathic group, serum cholesterol level and foot fissures were significantly positively correlated with PPP (p=0.035), (p=0.025) respectively in the univariate analysis and (p=0.04), (p=0.029) respectively in the multivariate analysis.

Table I: Univariate and multivariate analysis for the parameters affecting neuropathy (Group A vs B)

	Univariate				#Multivariate			
	B	**SE**	**P**	**OR (95%C.I)**	**B**	**SE**	**p**	**OR (95%C.I)**
Urinary albumin creat ratio (c)	0.654	0.386	**0.090**	1.923 (0.903 – 4.098)				
eGFR	–0.029	0.011	**0.006***	0.972*(0.952 – 0.992)	–0.023	0.014	**0.107**	0.978 (0.951 – 1.005)
HbA1c	1.578	0.279	**<0.001***	4.846*(2.804 – 8.37)	1.439	0.291	**<0.001***	4.247*(2.398 – 7.525)
BMI								
Normal (R)	–	–	–	–				
Overweight	–0.575	0.814	**0.480**	0.563 (0.114 – 2.77)				
Obese	–0.533	0.760	**0.483**	0.587 (0.132 – 2.60)				
Smoking history	1.242	0.608	**0.041***	3.462*(1.052 – 11.38)	1.184	0.856	**0.170**	3.23 (0.605 – 17.163)
Duration of DM	1.268	0.379	**0.001***	3.55*(1.69 – 7.47)	0.135	0.568	**0.779**	1.171 (0.388 – 3.532)
Fundus examination	1.101	0.278	**0.001***	3.645*(1.757 – 7.559)	0.256	0.387	**0.570**	1.080 (0.828 – 1.408)
Cholesterol	0.004	0.004	**0.260**	1.004 (0.997 – 1.012)				
TG	0.001	0.002	**0.602**	1.001 (0.997 – 1.006)				

OR: Odd`s ratio, C.I: Confidence interval,

#: All variables with p<0.05 was included in the multivariate

*: Statistically significant at p < 0.05

Table II: Univariate and multivariate analysis for parameters affecting high peak planter pressure (n = 128)

Peak planter pressure	Univariate				#Multivariate			
	B	SE	P	OR (95%C.I)	B	SE	p	OR (95%C.I)
Fundus (c)								
Normal dilated vessels (R)	–	–	–	–				
NPDR	0.292	0.491	0.551	1.339 (0.512 – 3.503)				

PDR	0.263	0.629	0.676	1.301 (0.379 – 4.465)				
Urinary albumin creat ratio (c)	–0.075	0.461	0.870	0.928 (0.376 – 2.289)				
eGFR	0.008	0.011	0.505	1.008 (0.985 – 1.030)				
HbA1c	0.486	0.173	0.005*	1.626*(1.158 – 2.282)	0.259	0.236	0.273	1.295 (0.815 – 2.059)
Cholesterol	–0.003	0.005	0.501	0.997 (0.988 – 1.006)				
Triglycerides	0.001	0.003	0.672	1.001 (0.995 – 1.007)				
Neuropathy (Group A vs B(R))	1.821	0.535	0.001*	0.162*(0.057 – 0.462)	1.721	0.701	0.014*	5.591*(1.414 – 22.09)
BMI								
Normal (R)	–	–	–	–	–	–	–	–
Overweight	1.056	0.818	0.196	2.875 (0.579 – 14.3)	1.403	1.082	0.195	4.065 (0.488 – 33.90)
Obese	1.596	0.762	0.036*	4.933*(1.109 – 21.9)	2.217	1.054	0.035*	9.181*(1.164 – 72.41)
Smoking history	0.167	0.681	0.806	1.182 (0.311 – 4.487)				
Duration of diabetes	–0.348	0.436	0.424	0.706 (0.301 – 1.658)				
CAD history	–1.050	1.072	0.327	0.350 (0.043 – 2.86)				
Ulcers	–0.496	1.103	0.653	1.642 (0.189 – 14.2)				
Fissures	–1.555	0.485	0.001*	4.737*(1.832 – 12.25)	–1.647	0.538	0.002*	0.193*(0.067 – 0.553)

OR: Odd`s ratio, C.I: Confidence interval,
#: All variables with p<0.05 was included in the multivariate
*: Statistically significant at p <0.05

DISCUSSION:

Diabetic foot ulcers are caused by a combination of several risk factors[38], with significant contributing roles for elevated mechanical foot pressures and diabetic peripheral neuropathy.[39],[40] Our study revealed that HbA1c, duration of diabetes, smoking history, eGFR and finding on fundus examination were independently statistically significantly positively affecting neuropathy. Long-term substandard blood glucose control leads to increased levels of non-enzymatic glycosylation products in peripheral nerve peripheral neurons, which can increase the flux of the polyphenol pathway, activate protein kinase C and stimulate oxidative stress, enhance the formation of late glycosylation end products, and cause corresponding clinical symptoms such as peripheral nerve damage.[42] It has been demonstrated that microvascular complications also play an important role in the development of DPN. Diabetic nephropathy and retinopathy are also microvascular complications. This study confirmed that low levels of eGFR was independent risk factor for DPN. Similarly, Zhifang Li et al [41] showed that the duration of diabetes, HbA1c and eGFR were independent risk factors for DPN but in Zhifang Li et al study, HDL-C and 24h urinary albumin were also independent risk

factors for DPN which is different from our results, it could be due to diet and life style that may affect HDL during the follow up period in this study.

To the best of our knowledge, this is the first study aiming to assess the relation between peak plantar pressure and the presence of diabetic microvascular complications in T2DM patients. In our study regression analysis for factors affecting PPP for the whole sample univariate analysis showed that neuropathy, HbA1c, BMI and foot fissures were independently statistically significantly positively correlated with the PPP.

In Antonella Caselli et al [43] work, the multivariate regression analysis VPT showed significant difference ($p<0.05$). A significant correlation between forefoot peak pressures and age, duration of diabetes, BMI, NDS, VPT and first MTPJ and STJ mobilities was found ($P < 0.05$). However, in multivariate regression analysis, age, BMI, VPT, and the vertical component of the ground reactive force (GRF; the force generated by the foot-to-floor interaction) were the only factors that showed statistical significance ($P < 0.05$). For the rearfoot pressures, first MTPJ mobility, NDS, VPT, and the vertical force were the only parameters significantly related ($P < 0.05$). No correlation was found with age, duration of diabetes, BMI, and STJ mobility. In multivariate analysis, the only significant predictor of rearfoot pressures was the vertical component of GRF ($P < 0.001$). The difference between our results and Antonella Caselli et al results may be due to difference in methodology, they used neuropathy disability score classifying patients into four groups (no, mild, moderate, severe neuropathy), also they used F -scan mat system to measure dynamic plantar pressures.

The limitations of this study are that although quantitative peak plantar pressure assessment is more accurate at low setting resource, using colourful peak plantar pressure added to our knowledge So we recommend using quantitative peak plantar pressure in future studies, we recommend multicentric future studies rather than one center and also, we recommend using nerve conduction test for diagnosis of diabetic peripheral neuropathy.

CONCLUSION:

In conclusion, neuropathy, DNS score, HbA1c, BMI, smoking history, serum cholesterol level and foot fissures were independently statistically significantly positively correlated with the PPP. Furthermore, no significant relation between peak plantar pressure and diabetic nephropathy or retinopathy. In addition, HbA1C, diabetes duration, eGFR and DR are risk factors for diabetic neuropathy.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Original Article

Comparative Study between Available Laboratory Techniques for Monitoring Blood Sugar Control in Diabetic Patients with Proteinuric Diabetic Nephropathy

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Abstract

Background: Strict glycemic control in patients with diabetes decreases the incidence of diabetic complications, which can determine the quality of life and prognosis of such patients, so we attempted to compare the available laboratory techniques: glycated albumin and glycated hemoglobin with SMBG as a gold standard in monitoring the control of diabetic state in proteinuric diabetic kidney disease patients. **Patients & Methods**: This study included 60 type 2 diabetic patients classified to two groups (group I: 30 patients with different grades of albuminuria A2/A3 and group II: 30 patients without albuminuria A1) All participants were subjected to history taking, full clinical examination and routine investigations. 7-point SMBG regimen, testing blood glucose before and after each of the three meals and at bedtime over the course of 3 days was taken every month for 4 months. HbA1c was done by HPLC technique after 2 months from the beginning of the study and at the end of the study. Glycated albumin was done by turbidimetric immunoassay every 5 weeks.**Results**: There was a positive significant correlation between **glycated albumin** and **ACR** among the proteinuric group. There was a positive correlation between **SMBG** and **HbA1c** among the two groups of the study. There was a positive correlation between **HbA1c** and **eGFR. Conclusion:** HbA1c is affected by eGFR and renal function while glycated albumin is affected by the levels of ACR and proteinuria, so combined assessment of HbA1c and glycated albumin may be useful for glycemic evaluation in DKD patients.

Introduction

Diabetes mellitus (DM) is characterized by occurrence of microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (atherosclerotic cardiovascular) complications.(1) Diabetic kidney disease (DKD) is considered as one of the major micro-vascular problems of diabetes mellitus and has become the most general single cause of end-stage kidney disease. One of the earliest changes of renal function in diabetes is an increase in GFR, or hyperfiltration, which is observed in patients with type 1 as well as in many patients with type 2diabetes and is accompanied by an increase in renal size. The next observable change is the development of albuminuria. (2)

Strict glycemic control in patients with DM decreases the incidence of diabetic complications, which can determine the quality of life and prognosis of such patients. (3) There are many markers to be used to assess glycemic states in diabetic patients. (4)The International Diabetes Federation (IDF) recommends SMBG for achieving glycemic goals. (5) HbA1c is affected by a number of factors including uremia, anemia of multifactorial etiology, decreased levels of erythropoietin, and decrease in RBCs survival. CKD patients frequently receive erythropoietin, with the expectation of an increase in the production of RBCs and which may lead to an erroneous low HbA1C value. (6)

Glycated albumin, because of its shorter half-life (21 days) compared with glycated hemoglobin, could be used as a shorter-term glycemic control for diabetes. Glycated albumin could be influenced by many conditions, such as thyroid dysfunction, nephrotic syndrome and liver cirrhosis. Therefore a combined detection of HbA1C and glycated albumin may improve the efficacy of diagnosis and improvement of a novel therapeutic potential. Therefore we attempted to compare the available laboratory techniques: glycated albumin and glycated hemoglobin with SMBG as a gold standard in monitoring the control of diabetic state in proteinuric diabetic kidney disease patients. [7]

Patients & Methods

This study was composed of 60 type2 diabetic patients classified into two groups: Group I: 30 patients with different grades of albuminuria A2/A3 and Group II: 30 patients without albuminuria A1. All patients provided written informed consent before participation in this study.

Exclusion criteria:

Patients with known thyroid diseases, liver diseases, malignancy, alcoholic patients, patients on corticosteroid therapy, patients with other causes of anemia rather than diabetic kidney diseases including history of blood loss and history of blood transfusion four months before the study and patients with active inflammatory state were all excluded from the study.

Methods

All patients in the study were subjected to: a full history taking stressing on: duration of DM, management of DM, complication of DM (hypoglycemia, hyperglycemia, microvascular and macrovascular complications), history of any renal diseases (urinary tract infection, stones, and hematuria), history of thyroid diseases, history of recent excessive alcohol intake, history of recent steroid therapy and history of hepatic symptoms. Full clinical examination stressing on, Puffiness of eyelids, ascites and lower limb edema. laboratory investigations were done including; complete urine analysis, urinary albumin /creatinine ratio, serum urea and serum creatinine, estimated GFR (eGFR)byMDRDequation,serum.cholesterol,.triglycerides,.HDL.cholesterol.and LDL cholesterol, complete blood picture, serum uric acid, liver function tests (serum albumin, alanine transaminase, aspartate transaminase.), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum TSH.

7-point SMBG regimen, testing blood glucose before and after each of the three meals and at bedtime over the course of 3 days was done every month for 4 months.

HbA1c was done by HPLC technique after 2 months from the beginning of the study and at the end of the study.

Glycated albumin was done by turbidimetric immunoassay every 5 weeks.

Results

The study included 60 patients with type 2 diabetes mellitus. The patients were divided into 30 patients with albuminuria and 30 patients without albumniuria. Demographic, anthropometric, and laboratory parameteters among studied groups are summarized in table I

As illustrated in table II , there was no statistically significant difference in SMBG levels and HbA1c levels between the two groups

Table III and IV showed correlations between different parameters among the two groups of the study.

Table (I): Comparisons between the two studied groups regarding to demographic, anthropometric and laboratory parameters.

	Group I (n = 30)	**Group II (n = 30)**	**p**
Sex Male Female	14(46.7%) 16(53.3%)	13(43.3%) 17(56.7%)	0.795
Age	60.83 ± 8.99	54.57 ± 12.75	0.032*
CKD	8(26.7%)	0(0.0%)	FEp=0.005*
DR	25(83.3%)	4(13.3%)	<0.001*
Neuropathy	17(56.7%)	13(43.3%)	0.302
Hypertension	24(80.0%)	16(53.3%)	0.028*
Cardiac complication	11(36.7%)	7(23.3%)	0.260
History of DFI	1(3.3%)	0(0.0%)	FEp=1.000
PVD	0(0.0%)	1(3.3%)	FEp=1.000
ACR	1037.50 ± 1053.42	20.04 ± 8.58	<0.001*
Cholesterol	215.13 ± 58.78	207.17 ± 43.29	0.553
TG	146.27 ± 49.08	133.57 ± 42.40	0.288
HDL	37.10 ± 6.55	44.43 ± 10.35	0.002*
LDL	98.97 ± 13.82	88.27 ± 13.11	0.003*
S. albumin	3.93 ± 0.40	4.08 ± 0.23	0.076

Table (II):Comparisons between the two studied groups regarding to mean of SMBG, mean of HbA1c

	Group I (n = 30)	**Group II (n = 30)**	**p**
SMBG	176.3 ± 53.08	207.5 ± 64.94	0.058
HbA1c	7.76 ± 1.60	8.34 ± 1.83	0.198

Table (III): Correlations between different parameters in group I

Group I	R	p
SMBG & diastolic BP	0.396*	0.030*
HbA1c& eGFR	0.378*	0.040*
GA & ACR	0.497	0.005*
GA & albumin	–0.574	<0.001*
GA & weight	–0.485*	0.007*
Cr& TG	0.362*	0.050*
eGFR & LDL	–0.408*	0.025*
TG & pulse	0.373*	0.043*
HDL & diastolic BP	0.425*	0.019*
Cholesterol & systolic BP	–0.424*	0.020*
Diastolic BP & albumin	0.384*	0.036*
Weight & CRP	0.419*	0.021*

Table (IV): Correlations between different parameters in group II

Group II	R	p
SMBG & cholesterol	0.659*	<0.001*
HbA1c & cholesterol	0.648*	<0.001*
HbA1c & Urea	–0.384*	0.036*
HbA1c &S.cr	–0.434*	0.017*
HbA1c &TG	0.454*	0.012*
eGFR & systolic BP	–0.447*	0.013*
Cholesterol & albumin	–0.525*	0.003*

Discussion

Diabetes Mellitus (DM) is not a single disease, but a syndrome characterized by hyperglycemia that result from defects in insulin secretion or insulin sensitivity in target tissues or both.Diabetic kidney disease (DKD) is one of the most serious microvascular complications, which significantly impacts morbidity, mortality and quality of life

Today, SMBG is considered an important aspect of the management of glycemic Control. SMBG is widely and routinely applied in large clinical trials, where it is used to understand the glycemic state HbA1c is the most widely used and accepted test for monitoring glycemic control in individuals with diabetes. HbA1c is affected by a number of genetic, hematologic, and illness-related factors.

Serum glycated albumin (GA) was hypothesized to be an alternative marker for glycemic control in patients with diabetes, as it not affected by changes in the survival time of erythrocytes in case of type 2 diabetes with hemoglobinopathies

Thus, this prospective study aimed to compare the available laboratory techniques: glycated

albumin and glycated hemoglobin with SMBG as a gold standard in monitoring the control of diabetic state in proteinuric diabetic kidney disease patients.

In the present study, there was a positive significant correlation between glycated albumin and ACR and a negative significant correlation between glycated albumin and S. albumin among the proteinuric group. The results of the present study also showed no significant correlation between glycated albumin and ACR among the non proteinuric group which coincides with results of Viswanathan V et al. [8] Okada et al [9] disagree with our results, as they found negative correlation between glycated albumin and ACR in the nephrotic range of proteinuria only, with no relation between GA and ACR among non-nephrotic range of proteinuria. Also Inaba et al [10] found negative significant correlation between glycated albumin and serum albumin.

Also In the present study, there was no significant association between GA and eGFR in both the two groups of the study, which can be interpreted by the fact that GA may not be influenced by renal function and so glycated albumin might be a better marker of glycemic assessment in advanced CKD. This result coincides with results of Okada et al. [9]

In the present study, it has been found a positive correlation between eGFR and HbA1c among proteinuric group and a negative correlation between HbA1c and B. urea and S. creatinine among non proteinuric group which coincides with the results of Paisey R et al. [11]

There was significant difference between the two studied groups as regards the age (p=0.032). Proteinuric patients were older than non proteinuric one. This result was supported by Thakkar et al. [12] In the present study, there was a significantly increased prevalence of hypertension in the proteinuric group compared to the non proteinuric group. Also we found a positive correlation between diastolic blood pressure and level of HDL, albumin and mean of SMBG. Finally there was negative correlation between systolic blood pressure and both of cholesterol and eGFR. These findings were supported by many studies including Bonaa KH et al, Ahbap E et al. [13, 14]

In the present study and during evaluation of lipids profile, we found numerous findings. Firstly, we found a statistically significant differences between the two studied groups regarding HDL-C and LDL-C. LDL-C was higher in the proteinuric group than in non the proteinuric group but HDL-C was higher in non the proteinuric group than in the proteinuric group.

Secondly, in the proteinuric group we found a positive correlation between S. creatinine and TG, a positive correlation between heart rate and TG, a negative correlation between LDL and eGFR among the proteinuric group.

Finally, in the non proteinuric group, we found a positive correlation between cholesterol and both of SMBG and HbA1c, a positive correlation between hemoglobin and TG and a negative correlation between cholesterol and S.albumin. These results agree with a lot of studies such as Palazhy S et al and Al Jameil N et al. [15, 16]

In the present study, we found a positive correlation between weight and CRP and a negative correlation between weight and glycated albumin among the proteinuric group. These results coincide with the result of Okada et al, Miyashita et al. [17]

Conclusion

HbA1c is affected by eGFR and renal function while glycated albumin is affected by the levels of ACR and proteinuria, so combined assessment of HbA1c and glycated albumin may be useful for glycemic evaluation in DKD patients.

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Original Article

Study of Diabetic Foot Disease in Type 2 Diabetic Patients With Chronic Kidney Disease

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Abstract

Introduction*:** Diabetes mellitus is probably one of the earliest diseases known to man, type 2 DM is most common and is more vulnerable to microvascular complications such as diabetic neuropathy and diabetic nephropathy causing CKD which is an added risk factor for diabetic foot disease. ***Subjects and methods*:** This cross-sectional study included 300 type 2 diabetic patients (aged 30-70 years) with chronic kidney disease classified into 5 groups according to eGFR. Clinical examination and full diabetic foot examination was done to all study subjects. HbA1c, LDL-C, serum creatinine, and urinary albumin creatinine ratio (ACR) were measured for all study subjects. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI equation. ***Results*:** There was statistically significant difference between the five groups as regard DN score ($p<0.001$). The DNS was significantly higher in cases in group 4,5A and 5B CKD as compared with group1 and group2. ABI was significantly low in groups 4,5A and 5B as compared with groups 1 and 2. The mean serum cholesterol, TGs level, LDL level, creatinine level and UACR increased significantly with increasing the stage of CKD while the mean HBA1C and HDL level decreased significantly with increasing the stage of CKD. There was a statistically significant negative correlation between GFR, age, duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also there was statistically significant positive correlation between GFR with ABI, HbA1C and HDL. ***Conclusion: There is a strong association between the degree of renal impairment and DFS. Diabetic patients on dialysis treatment had a high prevalence of DF and most of them had one or more risk factors for developing an ulcer in the future.

Introduction:

The typical presentation of diabetic kidney disease is considered to include a long standing duration of diabetes, retinopathy, albuminuria without haematuria, and gradually progressive loss of eGFR. [(1)] Diabetic nephropathy is now the most common cause of chronic kidney disease (CKD). Both types of diabetes can lead to chronic kidney disease and eventually ESRD, but there is much higher prevalence of type 2 diabetes than type 1, often patients with ESRD have type 2 diabetes.[(2)]

Neuropathies are among the most common long term complications of diabetes, affecting up to 50% of patients.[(3)] Risk factors for the development of PN include diabetes duration, degree of hyperglycemia, hyperlipidemia, hypertension, and height .[(4)] Retinopathy and nephropathy are highly associated with PN, occurring in type 2 diabetic patients by 55% and 32%, respectively. [(5)] The definition of the diabetic foot has been described as infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease.[(6)]

Subjects & Methods:

The present study was conducted on 300 patients who were classified into five stages according to estimated glomerular filtration rate (e GFR). Patients of fifth stage (e GFR less than 15) were classified into dialysis group and no dialysis group.[(7)] Clinical assessment of the patients included blood pressure, body mass index (BMI), waist circumference (WC), the severity of peripheral

neuropathy by diabetic neuropathy score (DNS), skin color, hair and nails, ulcers(size, depth, site, discharge, margins, floor, type), checking appropriate foot wear. Also joint flexibility and deformities.[8] Neurological examination was done by tuning fork, deep tendon reflex of the ankle joints. Vascular examination was done by assessment of ankle brachial pressure index (ABPI). [7] Laboratory investigations included HbA1C, lipid profile, serum creatinine, eGFR (was calculated according to CKD-EPI formula), Urinary albumin creatinine ratio (UACR), complete urine analysis and ultrasound abdomen. [7]

Results:

Regarding demographic data of the study population, the mean age of the cases was 58.2±5.47 years and there were 114 males (38%) and 186 females (62%). The anthropometric measures of the study population; the mean body weight of the cases is 91.16 ± 9.43 kg, the mean waist circumference is 112.7 ± 27.03 cm and the mean BMI is 27.51 ± 4.87 kg/m^2.Also there were (18%) current smokers and ex-smokers (19.3%). The median duration of DM among the cases was 12.4 years with range between 3 and 25 years. According to the treatment regimen for DM, insulin was the most commonly used medications alone (38.3%) or in combination with metformin or sulfonylurea. Sulfonylurea is used alone in (29%) and metformin is used alone in (4.7%) while combined regimen (19.3%).

Regarding the past medical history of the cases HTN was present in (72%). CKD (40%), cerebrovascular stroke (12.7%) and coronary artery disease (39.3%). there were (10.7%) with previous hemodialysis, (13.3%) with previous amputation and (6%) with previous foot ulcers. The cases of study were distributed into 5 groups according to eGFR calculated in ml/min/m^2. There were 68 cases in group 1(GFR 60-89), 62 cases in group2 (GFR 45-59), 52 cases in group3 (GFR 30-44), 48 cases in group 4(GFR 15-29), 36 cases in group 5A (GFR <15 not on haemodialysis) and 34 cases in group 5B (GFR <15 on haemodialysis).

There was no statistically significant difference in the mean age, sex distribution and prevalence of smoking among the cases within the different subgroups. There was a statistically significant difference between the different subgroups in the mean weight, waist circumference and BMI (p= 0.003, 0.021 and 0.010).There was a significant increase in the weight, waist circumference and BMI with progression of the stage of CKD. There was a statistically significant difference in the duration of DM among the cases in the different subgroups (p=0.001).The cases with stage 5B CKD have the longest duration of DM. The cases in the different subgroups have statistically significant longer duration of DM as compared with the cases in group 1. The prevalence of HTN was high in the cases with stage 5A (94.4%) and stage 5B (94.1%) with statistically significant difference as compared with other groups. Also the prevalence of HTN was statistically significant higher in cases in stage 3 and 4 CKD as compared with the cases in stage 1 and stage 2 CKD.

Correlating the diabetic neuropathy score (DNS) and the ankle brachial index (ABI) between the cases within the different groups in the study, there was high statistically significant difference between the different study groups (p<0.001). The DNS was significantly higher in cases in group 4 CKD as compared with G1, in group 5A as compared with group 1 and 2, in group 5B as compared with group 1, 2 and 3. The ABI was significantly lower in cases in group 2 and 3 CKD as compared with G1.The ABI was significantly lower in group 4 as compared with group 1 and 2 ,in group 5A as compared with group 1, 2 and 3. In group 5B as compared with group 1 , 2, 3 and 4.

The cold skin, absent skin hair and nail changes in the form of fungal infection and thick yellow changes were significantly higher with increasing the stage of CKD. Also Increased incidence of foot deformities like hallux vulgus and flat foot in group 5A and group 5B. As regards of Charcot joint deformity, 2 cases in group 1 and 4 cases in group 4 CKD had Charcot joint deformity that didn't appear in other groups. There is statistically significant difference (p<0.001) and increase incidence of abnormal tuning fork, ankle reflex and limited joint flexibility with increasing the stage of CKD.

There was statistically significant difference in the HbA1c, TGs level, HDL, creatinine and UACR between the cases in the within the different study groups. The mean serum cholesterol, mean TGs level, mean LDL level, mean creatinine level and UACR increased with increasing the stage of CKD while the mean HbA1c and HDL level decreased with increasing the stage of CKD. The ultrasound changes in the kidneys within the cases in the different groups, all cases within group 1 had normal kidneys and (52.9%) of group 5B had grade IV nephropathy. increased cases of grade III nephropathy among group 4,5A,5B .

There is a statistically significant negative correlation between GFR, age, and duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also there is statistically significant positive correlation between GFR with ABI, HbA1c and HDL. The multilinear regression analysis, duration of DM and eGFR reveal statistically significant prediction ability with ABI. Table I

Table I: Multinomial regression analysis model for ankle brachial index.

	a (constant)	b (regression coefficient)	t	P value
Age	.002	.004	.050	0.960
Duration of DM	.003	-.356	-4.512	<0.001*
Weight	.025	.183	.097	0.923
Height	.014	-.022	-.053	0.958
waist circumference	.001	-.019	-.111	0.912
body mass index	.080	-.212	-.119	0.906
HBA1C	.012	-.152	-1.710	0.090
S.CHOLESTEROL	.002	.002	.023	0.982
S.TG	.006	-.064	-.627	0.532
LDL	.001	-.057	-.670	0.504
HDL	.003	.140	1.766	0.080
S.CREATININE	.030	-.001	-.005	0.996
e.GFR ml/min	.001	.342	2.330	0.021*
urinary albumin creatinine ratio (UACR)	.004	-.089	-.597	0.552

$y = a + bx$ where 'y' is the value of the outcome variable, 'x' is the value of the explanatory variable, 'a' is the intercept of the regression line and 'b' is the slope of the regression line

Discussion:

In the present study females were more common than males, In agreement with study of Akbari et al. [9] The present study showed that HTN was present in (72%)of cases. Also, there were 45 current smokers (18%) and 58 ex-smokers (19.3%).The median duration of DM among the cases was 12.4 years .Our results were supported by study of Dòria et al., as they found that the mean diabetes duration was 22.3 years (SD = 12.2 years). 83% of them had HTN. [10]

The current study showed that insulin was the most commonly used medications alone in (38.3%) and as regard the past medical history of the cases, CKD was the most common followed by coronary artery disease, previous hemodialysis, amputation, cerebrovascular stroke and previous foot ulcers. Our results were supported by He et al., 2017, study .More than 90% of patients received insulin therapy to control blood glucose. During the follow up period, (39.3%) of patients suffered from one or more cardiac and (or) cerebrovascular events. Over 50% of the patients with reduced eGFR suffered cardiac events, whereas only less than 30% of patients in the normal eGFR group had cardiac events. [11] In the study of Wolf et al., forty-six patients (5.1%) of their collective have active or a history of DFS (Diabetic foot syndrome) (defined as acute or previous ulcers or amputation because of DFS). [12]

As regard duration of DM, Cases with stage 5B CKD have the longest duration of DM. The prevalence of HTN was high in the cases with stage 5A (94.4%) and stage 5B (94.1%), in cases in stage 3 and 4 CKD. In the

study of Shaheena et al., group 1 included 80 patients with an active foot ulcer, mean age 57.5 ± 7.2 years that was significantly higher than the mean age of group 2, which was 43.2 ± 7.5 years. [13] No significant difference was found between both the groups with respect to BMI. However, Anitha Rani & Viswanathan found statistical significance were observed in age (P<0.001), gender (P<0.005) duration of diabetes (P<0.001) and duration of hypertension (<0.001) between subgroups. [14]

According to the International Working Group on the Diabetic Foot (IWGDF), DF is defined as the ulceration, infection and/or destruction of deep tissues below ankles in patients with diabetes and/or peripheral arterial disease. Complications affecting the lower limbs are among the most common manifestations of diabetes. [15]

The present study showed that with comparing parameters of DFS as diabetic neuropathy score (DNS), the ankle brachial index (ABI), absent tuning fork, absent ankle reflex, nail changes, cold skin temperature, absent skin hair and limited joint flexibility between the cases within the different groups, there was high statistically significant difference (p<0.001) and increase incidence with increasing the stage of CKD.

Our results were supported by study of Dòria et al., as they reported that the prevalence of foot complications was, from the highest to the lowest, PN (89.1%), moderate or severe PAD (64.2%), foot deformities (54.3%), previous ulcer (19.6%), DF (17.4%), and amputations (16.3%). finally, based on the IWGDF classification, out of 83 patients explored, 87% had some risk grade for suffering DF in the future.[10]Also supported by study of Anitha Rani & Viswanathan as they demonstrated that neuropathy was higher in group I (34.5 %) followed by group III (33 %) and group II (12 %) respectively (Group I: T2DM with CKD and DFI, Group II: T2DM with CKD, Group III: T2DM with DFI and without CKD and Group IV- T2DM without any complications). [14]Our results were in contrary with study of Shaheena et al., as they reported that there no statistically significant differences between both the groups with respect to the presence of retinopathy, the presence of ischemic heart disease, mean ankle brachial index.[13]

The showed current study, the mean serum cholesterol, mean TGs level, mean LDL level, mean creatinine level and UACR increased with increasing the stage of CKD while the mean HBA1C and HDL level decreased with increasing the stage of CKD. Our results were supported by Wolf et al. concluded that type 2 DM with diabetics' foot syndrome were significantly higher HbA1c and had a longer duration of diabetes compared with type 2 DM without diabetic's foot syndrome. [12] In the study of Mrozikiewicz-Rakowska et al., the univariate logistic regression analysis showed that CKD risk factors were the following variables: mean creatinine level, mean body weight, mean hips circumference, ischemic heart disease, hypertension and diabetic retinopathy. Each mg/dl more in creatinine serum level was increasing the risk of CKD development by 4.5%. The risk of CKD development was increased by 3.7% per each additional kg in weight. There was also observed an increase in CKD development risk by 6.3% for each additional centimeter in hips circumference. Moreover, CKD risk was increased by the coexistence of ischemic heart disease, hypertension and diabetic retinopathy, over 2.7-fold, 7.3-fold and 4.4-fold, respectively. [16]

There is a statistically significant negative correlation between GFR with age, duration of DM, weight, waist circumference, BMI, DNS, TGs, creatinine and UACR. Also, there is statistically significant positive correlation between GFR with ABI, HBA1C and HDL. With multi-linear regression analysis, duration of DM and GFR reveal statistically significant prediction ability with ABI. With multi-linear regression analysis, duration of DM and HDL reveal statistically significant prediction ability with DNS.

In the study of Ninomiya T, et al, they found that the risk for each outcome increased linearly with lower eGFR levels. Every 10 fold increment in baseline UACR, which corresponds approximately to a change from one clinical stage of albuminuria to the next was associated with a 1.6-fold, two-fold, and 3.3-fold higher, multivariable-adjusted risk of

cardiovascular events, cardiovascular death, and renal events, respectively.[17] In Lepantalo et al. study it was believed that the essential factor for DFU is a loss of renal function. Disturbance of glucose metabolism and production of glycogen is caused by damaging insulin binding to receptors that cause tissue insulin resistance, particularly in skeletal muscles.[18]

Wolf et al., demonstrated that compared to type 2 patients without DFS those with DFS were significantly older ($P < 0.005$), had a longer duration of diabetes ($P < 0.005$), higher serum creatinine levels ($P < 0.005$) and a lower eGFR ($P < 0.005$). Patients who smoked did not have DFS more frequently than non-smokers. There was a significant negative correlation between the Wagner stages and eGFR ($r = -0.104$, $P < 0.01$) as well as Armstrong stages and eGFR ($r = -0.125$, $P < 0.01$) in all patients with type 2 diabetes. Multivariate logistic regression analysis revealed a significant negative association between a 10 ml/min change in eGFR and DFS as well as diastolic blood pressure. [12]

Conclusion:

There was a strong association between the degree of renal impairment and DFS. Diabetic patients in dialysis treatment had a high prevalence of DF, and most of them had one or more risk factors for developing an ulcer in the future. Hypertension is the most common comorbidity of diabetes, insulin is the most common used anti diabetic medication followed by sulphonylurea. The most common macrovascular complications are coronary artery disease and cerebrovascular stroke. Deterioration of eGFR with the longer duration of diabetes causing Diabetic neuropathy score (DNS) and Ankle brachial pressure index (ABI) to decrease with eGFR decrease. High risk of fungal infection and foot deformities with increase stages of CKD. Ultrasound abdomen was normal at early stages of CKD also HbA1c, HDL decrease in delayed stages of CKD.TGs, creatinine and UACR increase in delayed stages of CKD.

Recommendations

Diabetic patients with CKD should be considered as a high risk group for the development of DFS and should therefore be regularly screened for DFS during every office visit. Early lesions need consequent management, such as offloading, antibiotic therapy and local wound care. Randomized clinical trials and the demonstration of a common mechanism that causes CKD and failure of the skin to heal are required.

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Original Article

Effect of Helicobacter Pylori Eradication on Glycemic Control in Type 2 Diabetes Mellitus

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ABSTRACT:

Background*: One of the most common infection worldwide is Helicobacter pylori (H pylori) infection, it causes many gastrointestinal disorders, including gastritis, gastric ulcers, and gastric malignancy.(1) Nowadays, diabetes mellitus is a major public health problem, as the number of diabetic patients all over the world is expected to rise to 642 million by 2040.(2) H pylori infection is associated with many extra digestive diseases. It has been suggested that there is a relation between H pylori infection and diabetes mellitus type 2 (T2DM).(3) A number of recent studies, have tried to find the relation between H pylori infection and diabetes, and whether the eradication of H pylori has an effect on glycemic control or not, but the results were conflicting.(4)* ***Objective:*** *Study the effect of H pylori eradication on glycemic control in type 2 diabetics.* ***Patients & Method:*** *Sixty type 2 diabetic subjects were confirmed to have H pylori infection by urea breath test, and their glycemic control was tested at baseline and 3 months after eradication.* ***Results:*** *Fasting blood sugar, HbA1c levels, and CRP were significantly reduced after H pylori eradication.* ***Conclusion:*** *H pylori infection affect blood glucose level and its eradication may improve glycemic control.*

Keyword: **H. Pylori, Glycemic Control, T2DM**

INTRODUCTION:

H pylori is a microaerophilic, gram negative organism, that causes many gastrointestinal diseases such as chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric cancer. H pylori is also involved in other extra digestive system affection such as cardiovascular and immune systems, recently it was found to be involved in insulin resistance and obesity.(5)

T2DM is now considered as a pandemic as it is responsible for death of about 3.8 million patients yearly worldwide.(6) Chronic hyperglycemia in diabetic patients may cause dysfunction in other systems like renal, cardiovascular and nervous system, and this is the main cause of death in those patients.(7) Insulin resistance, chronic inflammation, reduced insulin secretion, glucotoxicity and lipotoxicity are all pathogenic mechanisms involved in diabetes(3), if a relationship between H pylori and T2DM is proved, there will be new methods for prevention and treatment options for diabetes.

A number of studies has tried to find the link between H pylori infection and diabetes, and whether the eradication of the bacteria has an effect on the blood glucose level, or not, but the results were conflicting.(4)

PATIENTS:

Type 2 diabetic subjects were randomly selected from those who were registered at our outpatient clinic or admitted to our inpatient wards. During selection, diabetes was diagnosed and confirmed according to the diagnostic criteria established by the American Diabetes Association at the time of the study, (8) and no change in their diabetes treatment protocol during the study

Inclusion criteria:

Patients with T2DM above 18 years of age, with 18.5 > body mass index (BMI) < 40 kg/m^2, and confirmed to have H pylori infection were involved in the study.

Exclusion criteria:

Individuals with any of the following were excluded: type one diabetes, chronic liver or renal disease, hematological disorders, malignancy, pregnant and lactating women, allergy to any of the drugs used in the study, withdrawing from H pylori treatment during the study, current antibiotic therapy, H2 receptor blockers therapy, or proton pump inhibitors therapy in the preceding 12 weeks.

METHODS:

Study design

This study design was a prospective randomized clinical trial and conducted on 60 type 2 diabetic subjects proved to have H pylori infection by urea breath test, their fasting blood sugar and glycated hemoglobin A1c (HbA1c) were measured at baseline, and after 3 months from treatment with H. pylori triple therapy and confirmed eradication, their fasting blood sugar and HbA1c were assessed again.

The study was conducted at Medical Research Institute, Alexandria University, during the period from January 2021 to May 2021; the subjects enrolled in the study were selected from diabetic population routinely attending the outpatient clinic or admitted to the inpatient wards for follow up and treatment of their diabetes. All procedures A written informed consent, was obtained from every subject; and all procedures were approved by the Ethics Committee of our institute.

- Thorough clinical examination.
- BMI was calculated as body weight in Kg divided by height in m^2 according to WHO criteria.[9]
- Urea breath test was done using a 100-mg of 13C-urea given with a meal, breath samples were tested at baseline and after 30 minutes. The test was considered positive when the relative amount of 13CO2 increased > 4.0 δ 13CO2 ppm. [10]
- C- reactive protein (CRP) was assessed as a marker of inflammation.[11]
- Glycemic control was assessed by fasting blood sugar and glycated hemoglobin A1c (HbA1c).[12]
- H. pylori eradication treatment done by using triple therapy for 14 days (Esomeprazole 20 mg given twice daily + Clarithromycin 500 mg twice daily + Amoxicillin 1000 mg twice daily). Eradication was confirmed after 3 months from the end of treatment. Negative test means successful eradication.[13]

Statistical analysis of the data

Data Datawere fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov test was used to verify the normality of distribution of variables.

Paired t-test was assessed for comparison between two periods for normally distributed quantitative variables, While Wilcoxon signed ranks test was assessed for comparison between two periods for abnormally distributed quantitative variables. Significance of the obtained results was judged at value < 0.05.

RESULTS: According to the above mentioned inclusion/exclusion criteria, 60 H. pylori positive type 2 diabetic subjects were involved in the study, 50 subjects had successful eradication and completed the study with success rate 83.3%.

The demographic data of H. pylori positive diabetic subjects at baseline were: age (59.6 ± 12.8) years, and gender (58%females and 42%males), waist 96.8±11.6 (cm), weight 81.6±12.4 (Kg), BMI 29.8±5.2 (Kg/m2).

H. pylori eradication had an effect on parameters of glycemic control, as we found that fasting blood sugar was significantly higher in diabetic subjects before H pylori eradication (336.0 ± 201), than after H pylori eradication (187.2 ± 49.5), P= <001. (Table I)

HbA1c level was significantly higher in diabetic subjects before H pylori eradication (8.7 ± 1.4), than after H pylori eradication (8.4 ± 1.3), P= <001. (Table I)

CRP was reduced by the H. pylori treatment, as it was higher in diabetic subjects before H pylori eradication (1.6 ± 0.43), than after H pylori eradication (0.98 ± 0.30), P= 0.004 (Table I).

Table I: Blood sugar control and CRP before and after eradication of Helicobacter pylori

	Before	After eradication	P
Fasting blood sugar Mean ± SD	336.0 ± 201	187.2 ± 49.5	<0.001*
HbA1c Mean ± SD	8.7 ± 1.4	8.4 ± 1.3	<0.001*
CRP Mean ± SD	1.6 ± 0.43	0.98 ± 0.30	0.004*

DISCUSSION:

The relation between H pylori infection and diabetes is still under investigation. Generally, the prevalence of H pylori infection in older age is more than that in younger age group this was found in many previous studies,[14] in our study H pylori was prevalent in diabetic subjects between 46-72 years of age, this is because most of the diabetic patients were in the older age group, and it is known that the rate of infection increases 0.3-1% per year.[15]

Distribution of H pylori in this study showed more prevalence in female diabetic subjects (58%) in comparison to the male diabetic subjects (42%), in agreement with studies done by Ghadimi [16] and Marusic.[14]

Colonization of the stomach with H pylori causes a state of low grade inflammation which is the main pathogenic mechanism in gastric complications such as, chronic gastritis, peptic ulcer, and lymphoma, but it is also a contributing factor in extra gastric complications such as cardiovascular, neurological, autoimmune, thyroid and hepatic diseases.[17] This low grad inflammatory state is mediated through upregulation of many cytokines such as CRP, tumor necrosis factor α (TNF α), and interleukins.[18]

CRP is a protein that is synthesized in the liver after stimulation by interleukin 6 and TNF α, increased levels of CRP is usually found in obesity, diabetes, smoking, and coronary artery disease.[19] In the study of Masayuki,[20] CRP was higher in the group of patients that had current H pylori infection than in never, or past infected group of patients. Some studies found higher CRP levels in H pylori positive diabetics than in H pylori negative diabetics,[21] other studies found no change in CRP level after H pylori eradication.[22] In the present study, CRP level was reduced after H pylori eradication, confirming that the state of low grade inflammation was also reduced after eradication.

H pylori also induce hepatic insulin resistance through signaling of c-Jun/miR-203/SOS3 pathway.[23] In asymptomatic Japanese subjects, infection with H pylori was more in those with insulin resistance than in those without resistance, after adjustment of all confounding factors.[24] However, in a study on 308 Lebanese subjects there was no association between H pylori infection with insulin resistance and metabolic syndrome, and concluded that eradication of infection will not affect the metabolic state.[25] In addition, H pylori infection alters secretion of gastric hormones, as it reduces gherlin production and increases leptin production, these changes lead to development of insulin resistance, and abnormal insulin secretion, which in turn affect glycemic control in diabetic patients.[26]

It was reported that eradication of H pylori can improve glycemic control, several studies showed reduction of fasting blood sugar and decrease in HbA1c after eradication, and attributed these results to decrease in pro-inflammatory factors.[27, 28]

In the study of Zojaji, H pylori eradication improved mean HbA1c and metabolic states of diabetic patients.[29] On contrary, De Luis in 2001 didn't find any change in HbA1c level after H pylori eradication.[30] In a study on 141 diabetic patients and 142 non diabetic subjects; there was no change in fasting blood glucose or in HbA1c after H pylori eradication.[31]

In the present study, There was significant reduction in the fasting blood sugar and in HbA1c levels after 3 months of H pylori eradication, together with the reduction in CRP level, which means that the cause of better glycemic control after H pylori eradication can be due to elimination of the source of inflammation and its subsequent mediators and cytokines that affect glucose metabolism.

CONCLUSION:

Helicobacter pylori eradication can improve glycemic control in uncontrolled diabetic patients, and it may be beneficial for diabetic patients to be checked for H pylori infection and to encourage eradication.

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Original Article

Anticitrullinated Protein Antibodies: Biomarker of Diagnosis & Prognosis in Elderly Rheumatoid Arthritis Patient with and Without Cognitive Impairment

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ABSTRACT:

INTRODUCTION: *Cognitive impairment is one of the most common comorbidities in elderly rheumatoid arthritis patients (RA). Possible etiological mechanisms of cognitive decline in aged rheumatoid arthritis, including chronic systemic inflammation affecting all organs, increased dysfunction of decreased substance use, and poor quality of life. Old RAs are associated with falls, cognitive impairment, and frail geriatric syndrome. The challenge in managing older patients with RA is usually that older people have significant comorbidity. Cognitive screening may be a useful tool for identifying subgroups to be further investigated for comorbid cerebrovascular disease. Anti-citrullinated protein antibody (ACPA) is a serological biomarker associated with early, rapidly progressing rheumatoid arthritis.* ***AIM OF THE WORK:*** *To assess the role of ACPA in elderly rheumatoid arthritis patients, to describe clinical, laboratory characteristics of disease activity, functional status, to determine the prevalence of cognitive impairment and the association of the determinants with the ACPA status.* ***SUBJECTS****: Sixty elderly patients with rheumatoid arthritis of both sexes aged ≥ 65 years fulfilling the 2010 EULAR /ACR classification criteria for rheumatoid arthritis recruited from the geriatric outpatient clinics were included in a cross-sectional study, with exclusion of patients with severe life-threatening disease, dementia, cancer or viral hepatitis.* ***METHODS:*** *Full medical history taking and thorough comprehensive geriatric assessment (CGA). Laboratory tests include CBC, FBS, 2hr PP, thyroid function tests, lipid profile, kidney function tests, ESR 1st hour, CRP, RF, liver function tests, uric acid, BMI categorized as normal, overweight and obese. Anticitullinated protein antibodies (ACPA) measured by ELISA technique. Disease activity assessment using DAS-28 CRP. Functional status assessment using HAQ score. CGA including function, mobility, cognitive, depression, fall risk, nutrition, full medication review and frailty index assessment. Plain X-ray of both hands and knees as a part of comorbidity assessment.* ***RESULTS:*** *Sixty elderly rheumatoid arthritis patients with cognitive impairment showed elevated anti-CCP titer. There was a marked increase in the number of the adverse outcomes scores in the elderly such as pain, mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, depression risk, frailty risk, mobility risk, and increased risk of comorbidities as elevated blood pressure, kidney, liver functions impairment, elevated ESR, CRP, ANA, FBS, 2hPP, uric acid and lipid profile.* ***CONCLUSION:*** *Since anti-CCP titre has a high specificity in the elderly, it can be used as a diagnostic and predictive biomarker in elderly rheumatoid arthritis patients with cognitive impairment.*

Keyword: Anti-cyclic citrullinated peptide CCP), Rheumatoid Arthritis, Cognitive dysfunction*.*

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, inflammatory disease characterized by chronic inflammation of the synovial joints leading to a progressive joint destruction. RA may involve both the vascular and nervous systems.[1,2] There is an increased risk of cognitive dysfunction, especially in elderly RA patients with long-standing disease [3]. Depression and anxiety are present in two-third of RA patients [4-6]. Cognitive function includes orientation, attention, concentration, judgment, problem solving, memory, verbal, visual, spatial and executive functions.[7-8] RA patients may significantly underperform on cognitive function tests compared to controls.[7,9-13] Even mild cognitive impairment may influence the functional capacity and quality of life of RA patients.[7,11,14,15] It affects reactivity to pain, compliance to and effectiveness of therapy.[7] In general, inflammation itself may also affect the brain.[6,7,13] Accelerated atherosclerosis and increased cardiovascular pathology also driven by systemic inflammation [11,15-17] may cause cognitive impairment in RA. Elderly RA is associated with the geriatric syndromes of falls, cognitive impairment, and frailty. A challenge when dealing with an elderly patient with RA is that the elderly usually has a significant comorbidity. Cognitive screening might be a useful tool to identify subgroups to be further investigated for cerebrovascular comorbidities. Pain, stress, fatigue, sleep disturbances, depression and anxiety may also be involved in RA associated cognitive decline.[5,7,11] Methotrexate, corticosteroids and biologics have been associated with cognitive impairment [7,18,19] As inflammation is involved in cognitive dysfunction in RA , the control of disease activity may be beneficial for the patients.[20, 21]

AIM OF THE WORK:

General Objectives: The aim was to assess the role of ACPA in elderly rheumatoid arthritis patients., **Specific Objectives:** Was to describe clinical, laboratory characteristics as well as functional status in elderly RA patients according to ACPA status, to describe the clinical , laboratory indices of disease activity , functional health status , to determine the prevalence of cognitive impairment and concurrent geriatric syndrome as a comorbidity in the elderly and their association with the ACPA status.

SUBJECTS:

Inclusion criteria: Sixty elderly patients with rheumatoid arthritis of both sexes aged ≥65 years fulfilling the 2010 EULAR / American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis recruited from the geriatric medicine unit and outpatient clinics of the main Alexandria university hospital were included in a cross-sectional study. **Exclusion criteria:** Patients with severe life-threatening disease, severe dementia, and those with past history of cancer or viral hepatitis. An informed consent was taken from all patients prior to connecting the study according to the Helsinki declaration. **Data collection:** Prior to baseline examination in the clinic each patient was interrogated thoroughly using a questionnaire. Data on extra-articular features, comorbid conditions and treatment records was collected Comorbid conditions, using the Charlson comorbidity index (CCI) to summarize the medical comorbidities. CCI sum is calculated according to the number of morbidities affecting the individual. For each morbidity, a number of points are allocated and the sum of these points gives an overall score. This sum can be used in conjunction with the patient's age as the Charlson score to calculate a probability of survival.[22]

METHODS:

1-Full medical history taking with specific stress on age, sex, duration of mourning stiffness, number of swollen and tender joints, history of smoking, drug history especially Methotrexate.[23]

2-General examination for detection of extra-articular manifestations associated with rheumatoid arthritis; as skin (rheumatoid nodules), nervous system, and cardiac examination for detection of any cardiac abnormalities as a part of comorbidity assessment.

3-Laboratory tests: Complete blood count and differential count,[24] fasting and 2 hours postprandial blood glucose, blood urea, serum creatinine,[25] ESR 1st hour, CRP,[26] SGPT, SPOT.[27]

4-Immunological Profile: Rheumatoid Factor (RF) titre [28], and Anticitrullinated Protein Antibody (ACPA) measured by ELISA technique.[29]

5-Determination of disease activity using disease activity score-28 (DAS-28) based on CRP (DAS-28-CRP) [30], Functional and Quality of Life (QoL) assessment scores using Health Assessment Questionnaire (HAQ) score. [31,32]

6-BMI assessment according to the WHO criteria and categorized as normal, overweight and obese

7-Comprehensive Geriatric Assessment (CGA): Functional assessment using Katz activities of daily living (ADLs),[33] Mobility assessment using the timed "Get up and Go Test ", Cognitive assessment using the Mini Mental State Examination (MMSE),[34] Depression assessment using the Geriatric Depression Scale (GDS-15),[35] Fall risk assessment using Fall Risk Checklist, Nutritional assessment using the Mini Nutritional Assessment (MNA), [36] Frailty assessment using Frailty Index Measurement,[37] and Full Medication Review

8-Ophthalmologic examination was performed for all elderly RA patients.

9-Echocardiography to detect any cardiac abnormalities in elderly RA patients.

10-Plain X-ray of both hands and knees joints as a part of comorbidity assessment.

Statistical Analysis of The Data: Data were fed to the computer and analyzed using IBM SPSS software package version 20.0, Armonk, NY: IBM Corp. Comparison between different groups regarding categorical variables was tested using Chi-square test . When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality. For normally distributed data, comparison between more than two populations were analyzed using F-test (ANOVA) and Post Hoc test (Scheffe).

For abnormally distributed data, Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Significance of the obtained results was judged at the 5% level. Differences of ($P < 0.05$) were considered statistically significant.

RESULTS: Table (I): Distribution of the studied cases according to demographic data. Table (II): Distribution of the studied cases according to musculoskeletal examination. Table (III): Distribution of the studied cases according to different disease comorbidities. Table (IV): Descriptive analysis of the studied cases according to neurological, cardiovascular and chest examination findings. Table (V): Distribution of the studied cases according to immunological and radiological findings. Table (VI): Distribution of the studied cases according duration of the disease symptoms. Table (VII): Distribution of the studied cases according to comprehensive geriatric assessment scores.

Table(I): Distribution of the studied cases according to demographic data (n=60).

Age (years)	
- Min-Max	62.00-72.00
- Mean ± SD	67.63±2.31
- 95% CI for mean	67.04-68.23
Sex	
- Males	26 (43.33%)
- Females	34 (56.67%)
Marital status	
- Married	40 (66.67%)
- Divorced	9 (15.00%)
- Widowed	11 (18.33%)
Residency	
- Alexandria	55 (91.67%)
- Kafr elshiekh	1 (1.67%)
- Kafr eldawar	3 (5.00%)
- Abo elmatameer	1 (1.67%)
Occupation	
- Not working	9 (15.00%)
- Worker	15 (25.00%)
- Professional	18 (30.00%)
- retired	3 (5.00%)
- Semiprofessional	4 (6.67%)
- Housewife	11 (18.33%)
Smoking status	
- Non smoker	34 (56.67%)
- Smoker	26 (43.33%)
Education	
- Illiterate	8 (13.33%)
- Primary School	1 (1.67%)
- Preparatory school	1 (1.67%)
- Secondary school	26 (43.33%)
- University	24 (40.00%)
WHO Classification	
- 18.5-24.9 (Normal weight)	15 (25.00%)
- 25.0-29.9 (Overweight)	25 (41.70%)
- 30.0-34.9 (class I Obesity)	18 (30.00%)
- 35.0-39.9 (class II obesity)	2 (3.33%)
- > 40.0 (class III Obesity)	0 (0.00%)

CI: Confidence Interval

Table (II): Distribution of the studied cases according to musculoskeletal system examination.

Joint pain	60 (100.00%)
Spinal pain	52 (86.67%)
Fatigue	14 (23.33%)
Stiffness	58 (96.67%)
Skin rash	3 (5.00%)
Hyperpigmentation	7 (11.67%)
Xanthelasma	2 (3.33%)
Musculoskeletal Swelling	
- MCP joints	7 (11.67%)
- PIP joints	3 (5.00%)
- Wrist joints	2 (3.33%)
- Elbow joints	2 (3.33%)
- Shoulder joints	1 (1.67%)
- Ankle joints	1 (1.67%)
Musculoskeletal Deformity	
- Knee deformity	1 (1.67%)
- Foot deformity	4 (6.67%)
- Hand deformity	12 (20.00%)
- Wrist deformity	1 (1.67%)
- Joint deformity	18 (30.00%)
Limited Movement	
- MCP	6 (10.00%)
- PIP	3 (5.00%)
- Hand	2 (3.33%)
- Elbow	4 (6.67%)
- Ankle	4 (6.67%)
- Wrist	6 (10.00%)
- Shoulder	1 (1.67%)
Stiffness	
- MCP	1 (1.67%)
- PIP	1 (1.67%)
- Hand	1 (1.67%)
- Wrist	1 (1.67%)
- Ankle	1 (1.67%)
Pain	
- MCP	1 (1.67%)
- Wrist	1 (1.67%)
- Ankle	1 (1.67%)
- Shoulder	1 (1.67%)
- Knee	1 (1.67%)
Tenderness	
- Wrist	1 (1.67%)
- PIP	1 (1.67%)
- Shoulder	1 (1.67%)

Table (III): Distribution of the studied cases according to different disease comorbidities

Diabetes mellitus	14 (23.33%)
Hypothyriodism	1 (1.67%)
Hypertension	25 (41.67%)
Pyelonephritis	1 (1.67%)
Recurrent UTI	4 (6.67%)
Eyes	
- Normal	30 (50.00%)
- Wearing glasses	30 (50.00%)

Table (IV): Descriptive analysis of the studied cases according to neurological, cardiovascular and chest examination findings

Neurological	
- Normal	48 (80.00%)
- Abnormal	12 (20.00%)
○ Numbness of one side	5 (8.33%)
▪ Left	3 (5.00%)
▪ Right	2 (3.33%)
○ Lower limb numbness	3 (5.00%)
○ History of stroke	7 (11.67%)
○ Side Weakness (left)	1 (1.67%)
Cardiovascular and Chest	
- Tachycardia	1 (1.67%)
- Palpitation	11 (13.33%)
- MI	3 (5.00%)
- Aortic stenosis	1 (1.67%)
- Dyspnea on excretion	8 (13.33%)
- COPD	2 (3.33%)

Table (V): Distribution of the studied cases according to immunological and radiological findings

APCA	
- Negative	0 (0.00%)
- Positive	60 (100%)
RF	
- Negative	4 (6.67%)
- Positive	56 (93.33%)
CRP	
- Normal	13 (21.67%)
- Elevated	47 (78.33%)
ESR	
- Normal	13 (21.67%)
- Elevated	47 (78.33%)
Hepatitis Marker	
- Negative	60 (100%)
- Positive	0 (0.00%)
Plain X rays	0 (0.00%)
CT Chest	0 (0.00%)
Echo/ ECG	
- Normal	55 (91.67%)
- Left Ventricular Hypertrophy	2 (3.33%)
- Sinus Tachycardia	3 (5.00%)
U/S Abdomen	0 (0.00%)
BMI (kg/m^2)	
- **Min-Max**	21.00-35.00
- **Mean ± SD**	27.18±4.10
- **95% CI for mean**	26.12-28.24

CI: Confidence Interval

Table (VI): Distribution of the studied cases according to duration of disease symptoms

Duration of stiffness score	
- Non specific	32 (5.33%)
- Less than one hour	28 (46.67%)
Duration of stiffness attack (hour)	
- Min-Max	0.25-1.50
- Mean ± SD	0.49±0.378
- 95% CI for mean	0.35-0.63
Morning stiffness	12 (20.00%)
Duration of suffering of stiffness (Months)	
- Min-Max	2.00-6.00
- Mean ± SD	4.00±1.83
- 95% CI for mean	1.09-6.91
Duration of suffering of diabetes (years)	
- Min-Max	10.00-15.00
- Mean ± SD	13.33±2.89
- 95% CI for mean	6.16-20.50
Duration of suffering of hypertensive (years)	
- Min-Max	3.00-10.00
- Mean ± SD	7.29±3.68
- 95% CI for mean	3.88-10.69
Duration of MI (years)	
- Min-Max	0.00-5.00
- Mean ± SD	0.63±1.77
- 95% CI for mean	-0.85 – 2.10
Duration of CHF (years)	
- Min-Max	0.00-3.00
- Mean ± SD	0.38±1.03
- 95% CI for mean	0.17 – 0.92

CI: Confidence Interval

Table (VI): Distribution of the studied cases according to CGA scores

Katz ADL index	
- Min-Max	2.00 – 12.00
- Mean ± SD	6.88±2.78
- 95% CI for mean	6.17-7.60
MNA Screening Score	
- Min-Max	4.00-16.00
- Mean ± SD	10.50 ± 2.19
- 95% CI for mean	9.93-11.07
Geriatric Depression Scale (GDS)	
- Min-Max	0.00 - 11.00
- Mean ± SD	9.00 ±1.80
- 95% CI for mean	8.54-9.46
MMSE (total points)	
- Min-Max	9.00-28.00
- Mean ± SD	18.03±5.10
- 95% CI for mean	16.71-19.38
FRF (total points)	
- Min-Max	0.00– 10.00
- Mean ± SD	5.78±1.914
- 95% CI for mean	5.29-6.28
CGA Katz ADL questionnaire out of 12	
- Min-Max	0.00– 6.00
- Mean ± SD	3.31±2.77
- 95% CI for mean	1.83-4.79
MMSE questionnaire out of 30	
- Min-Max	0.00-28.00
- Mean ± SD	16.93±12.46
- 95% CI for mean	10.03-23.84
GDS questionnaire out of 15	
- Min-Max	0.00-12.00
- Mean ± SD	5.79±4.58
- 95% CI for mean	3.14-8.43
MNA for nutrition questionnaire	
- Min-Max	0.00-13.00
- Mean ± SD	6.93±4.70
- 95% CI for mean	4.22-9.64
DAS measurement	
- Min-Max	3.75-5.22
- Mean ± SD	4.52±0.54
- 95% CI for mean	4.10-4.94
Mobility assessment Get and Go test (min)	
- Min-Max	0.00-20.00
- Mean ± SD	15.60±5.78
- 95% CI for mean	11.47-19.73

CI: Confidence Interval

DISCUSSION:

Cognitive decline is a deterioration of intellectual and learning abilities and related memory problems, and is often associated with behavioral alterations, which prevents patients from carrying out the most common daily activities, such as maintaining normal productive interpersonal relationships, communicating, and leading an autonomous life. The aim was to assess the role of ACPA in elderly rheumatoid arthritis patients, to describe clinical, laboratory characteristics as well as functional status according to their ACPA status, and to determine the prevalence of cognitive impairment and concurrent geriatric syndrome as a comorbidity in elderly rheumatoid arthritis patients. In this cross sectional study, sixty elderly patients with rheumatoid arthritis of both sexes aged ≥ 65 years fulfilling the 2010 EULAR/American College of Rheumatology (ACR) classification criteria for rheumatoid arthritis were included, with exclusion of patients with severe life-threatening disease, severe dementia, and those with past history of cancer or viral hepatitis. Screening for comorbidities was initially carried out as part of the interrogation. A questionnaire was used to assess functional disability, quality of life, visual analogue scale (VAS) for spinal pain, joint pain, global status, fatigue, duration of morning stiffness, review of the systems, falls and cardiovascular risks. Monitoring of comorbidities and risk factors as cardiovascular disease detected by blood pressure measurement, blood glucose, lipid profile, kidney and liver function assessment was performed. Monitoring for infections including Hepatitis B, C was done. Opthalmological examination, echocardiogram and X- ray of the affected joints was carried out for all elderly rheumatoid arthritis patients.

The emerging body of data suggests that clinical, psychological, and biological factors may contribute to the pathogenesis of cognitive decline in RA, including cardiovascular complications, chronic pain, depression, inflammatory factors, drug side effects, and genetics which also were documented by Van der Woude, et al.[38] Comprehensive geriatric assessment (CGA) is a multidisciplinary diagnostic and therapeutic process to determine the medical, psychological, and functional capabilities of an older person to develop a coordinated and integrated plan for treatment and follow-up[39]. CGA is the gold standard for the assessment and management of an elderly person with complex health and social care needs, and those living with frailty. Elderly people with multimorbidity or frailty may benefit from CGA.

Our results demonstrated that sixty elderly rheumatoid arthritis patients with cognitive impairment showed elevated anti-CCP titer. There was a marked increase in the number of the adverse outcomes scores in the elderly such as pain, mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, depression risk, frailty risk, mobility risk, and increased risk of comorbidities as elevated blood pressure, kidney, liver functions impairment, elevated ESR, CRP, ANA, Anti-CCP Abs, FBS, 2hPP, uric acid and lipid profile.

The exact relationship between RA and cognitive impairment remains contentious [40]. Cognitive impairment is one of the most common comorbidities found in RA, ranging between 38 and 71% [41, 42]. The pathogenic mechanisms of cognitive decline in RA are unknown [43]. Elderly onset RA seems to have a characteristic clinical pattern and perhaps biological profile different to that of early onset RA.[44,45] Working ability is one of most important goals for RA and also non-frail status should be goal of elderly RA, since it is associated with health expectancy.[46] Anticitrullinated protein antibodies (ACPAs) are serological biomarkers associated with early, rapidly progressing rheumatoid arthritis (RA), including more severe disease and joint damage. ACPA testing has become a routine tool for RA diagnosis and prognosis reviewed by Brink M et al.[47] Disease activity, which is reflected by tender and swollen joint counts, levels of acute phase reactants, and patient's and physician's global assessments, is a good predictor of damage and physical disability, and an outcome measure, which is used to evaluate health outcome in clinical

studies of patients with RA reviewed by Balsa A et al,[48]. A number of mechanisms have been proposed for the pathogenesis of cognitive impairment in RA including a chronic systemic inflammatory process involving all organs. Intact cognitive function is important for executing several basic tasks in people with chronic diseases, including RA documented by Mueller R, et al.[49]

Michael J et al, documented no association between rheumatoid arthritis and cognitive impairment in a cross sectional large national probability sample in elderly patients [50]. High prevalence of cognitive impairment among elderly RA patients was observed. Systemic inflammation is a well-established risk factor for cognitive impairment, which is found to be a strong predictor of poor physical and mental outcomes in RA. Cognitive impairment was not related to clinical, treatment features or disability. More studies are necessary to determine the clinical impact of cognitive impairment in elderly RA patients.[51,52] Elderly RA patients are at a particular risk due to increased cardiovascular morbidity.[53,54] It has been suggested that RA therapy might have a predictive effect on cognitive function, further supported by a German study where effective treatment significantly improves the mental component of the Short Form 36 (vitality, social functioning , role-emotional and emotional well-being) [53,55]. However, cognitive impairment in RA could be underestimated in clinical practice and might undermine the efficacy of RA therapy in the elderly by affecting their compliance to therapy [56]

CONCLUSION:

During disease progression anti-CCP titer in elderly rheumatoid arthritis patients with cognitive impairment was elevated. It was expected since anti-CCP has a high specificity for rheumatoid arthritis and become positive in the elderly with a high predictive value. However, in early stages of cognitive impairment, we could not use this biomarker as a diagnostic test. It needs more studies to confirm the role of anti-CCP antibody production in elderly rheumatoid patients without cognitive impairment.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Original Article

Comprehensive Geriatric Assessment in Elderly Patients with Rheumatic Musculoskeletal Diseases.

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Abstract:

Introduction: Management of geriatric patients with rheumatic diseases is difficult due to associated comorbidities such as diabetes mellitus, chronic obstructive lung disease and hypertension, variation in autoantibody profile, polypharmacy and atypical clinical manifestations. Comprehensive geriatric assessment (CGA) is a multidimensional process designed to assess an elderly patient`s functional ability, physical health, cognitive and mental health. CGA could thus improve patient management and satisfaction. **Aim of The Work:** Was to assess the prevalence of geriatric health problems in elderly patients with common rheumatic musculoskeletal diseases, to determine the association between health problems through comprehensive geriatric assessment and to determine the association between comorbidity and disease activity. **Subjects:** One hundred elderly patients ≥ 65 years of age, with rheumatic musculoskeletal conditions recruited from the geriatric outpatient clinics were **included** in a cross-sectional cohort study with **exclusion** of patients with life threatening disease, dementia, cancer or viral hepatitis. **Methods:**1- Full medical history taking, general physical and musculoskeletal examination. 2- Laboratory tests include CBC, FBS, 2hr PP, thyroid function tests, lipid profile, kidney function tests, ESR 1st hr, CRP mg /dl, Rheumatoid factor (RF), liver function tests, uric acid and ANA. 3-Anticitullinated protein antibodies (ACPA) by ELISA technique. 4- Disease activity assessment using DAS-28 CRP. 5- Functional status assessment using HAQ score. 6-Comprehensive geriatric assessment (CGA). 7-Plain X-ray of both hands and knees possible OA. **Results:** There was a marked increase in the number of the adverse outcomes scores in the elderly such as pain, mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, depression risk, frailty risk, mobility risk, and increased risk of comorbidities as elevated blood pressure, kidney, liver functions impairment, elevated ESR, CRP, ANA, Anti- CCP Abs, FBS, 2hPP, uric acid and lipid profile. **Conclusions:** The management of musculoskeletal disorders requires not only the use of available tools but also the development of recent new tools for prediction, diagnosis, monitoring, and prognosis of these disorders and their combination.

Key Words: Comprehensive geriatric assessment (CGA), Comorbidities, Elderly patients.

Introduction:

The world population is aging, as we are currently faced with unprecedented rise in the number of older adults.(1) Individuals of ≥ 65 years of age is increasing in numbers globally, and by 2050, the global population aged ≥ 65 years is predicted to reach over 1 billion.(2) In this rapidly expanding older portion of the national population, one of the major changes that commonly accompany the aging process is an often profound disruption of an individual's daily function.(3) The global rise in aging is causing higher rates of osteoporosis, a condition that reduces bone density and quality.(4) Aging leads to changes in bone metabolism that increase the risk of osteoporosis. Furthermore, age-related nutritional deficiencies, reduced muscle mass, and mobility increase the risk of falls and / or disability. (5) Osteoarthritis increases with age due to wearing down of protective joint cartilage.(6,7) The rising number of older adults has increased osteoarthritis rates, with estimates of 12% to 40% across different regions.(8,9) Osteoarthritis is associated with frailty, falls, and impaired mobility in the elderly . Moreover, it is linked to chronic pain and disability. Osteoporosis and osteoarthritis form the bulk of musculoskeletal morbidity in older adults. Effect functionality, quality of life, and lead to complications like falls, incontinence, and depression. Studies reports high prevalence of vitamin D deficiency amid poor socio-economic conditions and nutritional deficiencies with low bone density.(10) Geriatric medicine concern with older people who are getting frailer and have a number of chronic medical issues.(11) The core concepts of geriatric medicine have changed little and described as the 'geriatric giants' (incontinence, immobility, intellectual impairment, instability.(12) The term 'giant' here refers to both the frequency of the problem and the burden on the individual. What is clear, however it is framed, that older people have complex multisystem disease overlaid on a normal ageing process that gradually reduces their ability to maintain homeostasis. (13) In order to provide coordinated management of such complex conditions, a logical framework for assessment and management of the patient is required. This framework is termed the comprehensive geriatric assessment (CGA). There is no single treatment or intervention for the management of frail older adults, but doing nothing can lead to progressive physical and mental decline. (14) Therefore, a detailed assessment of each patient's potential modifiable facets is needed. It is well recognized that, in older people, there is often a large overlap between symptoms caused by disease, by normal ageing, by accelerated ageing and by the management given for this various condition. (15) CGA is a multidimensional interdisciplinary diagnostic process focused on determining a frail person's medical, psychological and functional capability in order to develop a coordinated and integrated plan for treatment and long-term follow-up. (16) As such it is firmly rooted in the biological, psychological and sociological process for thinking about patients and their conditions. CGA goes beyond simply managing the problem that the person has presented with and is considered as a proactive investigation and management process. (17)

Inclusion criteria: One hundred elderly men and women ≥ 65 years of age, with rheumatic and musculoskeletal conditions **r**ecruited from the geriatric medicine unit outpatient clinics of the main Alexandria university hospital were included in a cross-sectional study. An informed consent was taken from all patients prior to connecting the study according to the Helsinki declaration.

Exclusion criteria: Patients with severe dementia or severe life-threatening disease were excluded from the study.

Data collection:

Prior to baseline examination in the clinic each patient was interrogated thoroughly using a questionnaire. Data on extra-articular features, comorbid conditions and treatment records was collected Comorbid conditions, using the Charlson comorbidity index (CCI) to summarize the medical comorbidities. CCI

sum is calculated according to the number of morbidities affecting the individual. For each morbidity, a number of points are allocated and the sum of these points gives an overall score. This sum can be used in conjunction with the patient's age as the Charlson score to calculate a probability of survival. [18]

Methods:

1-Full medical history taking including data on smoking status, marital status, level of education, history of fall (s) within the previous year, visual problems, hearing problems, presence or absence of urinary incontinence, sleep problems, fatigue, general physical examination comorbidities present and frequency including blood pressure measurement, cardiovascular disease, diabetes mellitus, GIT disease, COPD, eye disease, cerebrovascular disease, osteoporosis, osteoarthritis, gout, hyperlipidaemia, neurological, musculoskeletal examination pain, duration, site (knee, neck, back, ankle), duration of mourning stiffness and extra-articular manifestations on the heart, eye, inflammatory bowel disease, skin fibromyalgia and medications used, frequency, percentage of the various rheumatic diseases, neurological examination including muscle weakness, sacropenia, neuropathy, carpal tunnel syndrome, deformities, kyphosis and abnormal gait .

2-Laboratory Tests: Complete blood count and differential count, [19] fasting and 2 hrs post prandial blood glucose, blood urea, serum creatinine, [20] ESR 1st hr, CRP mg/dl, [21] SGPT, SPOT. [22]

4-Immunological Profile: Rheumatoid Factor (RF) titre,[23] and Anticitrullinated Protein Antibody (ACPA) measured by ELISA technique.[24]

5-Determination of disease activity using disease activity score-28 (DAS-28) based on CRP (DAS-28-CRP), [25] Functional and Quality of Life (QoL) assessment scores using short form-36 (SF-36), [26,27] Patient and Physician Global Assessment (PTGA), Health Assessment Questionnaire Disability Index (HAQ-DI).

6-BMI assessment according to the WHO criteria and categorized as normal, overweight and obese, Visual Analogue Pain Scale (VAS) to be measured for each patient.

7-Comprehensive Geriatric Assessment (CGA):

- Functional assessment using Katz activities of daily living (ADLs) [28]
- Mobility assessment using the timed "Get up and GoTest "
- Cognitive assessment using the Mini Mental State Examination (MMSE) [29]
- Depression assessment using the Geriatric Depression Scale (GDS-15) [30]
- Fall risk assessment using Fall Risk Checklist
- Frailty assessment using Frailty Index Measurement [31]

8-Ophthalmologic examination was performed for all elderly rheumatoid arthritis patients.

9-Echocardiography to detect any cardiac abnormalities in elderly rheumatoid arthritis patients.

10-Plain X- ray of both hands and knees for possible OA.

Statistical Analysis of The Data:

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0, Armonk, NY: IBM Corp. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality.

For normally distributed data, comparison between more than two populations were analyzed using F-test (ANOVA) and Post Hoc test (Scheffe).

For abnormally distributed data, Kruskal Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney test. Significance of the obtained results was judged at the 5% level. Differences of ($P< 0.05$) were considered statistically significant.

Results:

Table(I): Distribution of the studied cases according to Demographic Data (n=100). Table (II): Distribution of the studied cases according to Urinary Incontinence, Sleep Problems and duration of Morning Stiffness. Table (III): Descriptive analysis of the studied cases according to functional activity scores. Table (IV): Descriptive analysis of the studied cases according to ESR, CRP, FBS, 2h PP, renal functions, liver functions, lipid profile and blood pressure measurement. Table (V): Descriptive analysis of the studied cases according to RF, ANA and Anti- CCP Ab Table (VI): Relation between a questionnaire for health assessment and mobility assessment using the timed (sec). Table (VII): Relation between a questionnaire for health assessment and mini mental state examination (MMSE). Table (VIII): Relation between a questionnaire for health assessment and geriatric depression scale (GDS-15). Table (IX): Relation between a questionnaire for health assessment and frailty index measurement.

Table (I): Distribution of the studied cases according to Demographic Data (n=100)

	No.	%
Sex		
Male	48	48.0
Female	52	52.0
Age (years)		
Min. – Max.	65.0 – 82.0	
Mean ± SD.	69.99 ± 3.96	
Median (IQR)	69.0 (67.0 – 71.50)	
Marital status		
Married	60	60.0
Divorced	8	8.0
Widow	32	32.0
Smoking status		
Non smoker	64	64.0
Smoker	36	36.0
BMI (kg/m^2)		
Min. – Max.	19.23 – 32.48	
Mean ± SD.	26.35 ± 2.82	
Median (IQR)	26.38 (24.38 – 28.24)	

SD: **Standard deviation** IQR: **Inter quartile range**

Table (II): Distribution of the studied cases according to Urinary Incontinence, Sleep Problems and duration of Morning Stiffness.

	No.	%
Urinary Incontinence		
Absent	68	68.0
Present	32	32.0
Sleep Problems		
Absent	30	30.0
Present	70	70.0
Duration of Morning Stiffness		
Less than one hour	22	22.0
More than one hour	78	78.0

SD: **Standard deviation** IQR: **Inter quartile range**

Table (III): Distribution of the studied cases according to Functional Activity Scores.

Disease Activity Score of 28 joints (DAS-28)	**No.**	**%**
Low disease activity (<2.6 to 3.2)	4	4.0
Moderate disease activity (>3.2 to 5.1)	50	50.0
High disease activity (> 5.1)	46	46.0
Min-Max	2.50 - 6.80	
Mean ± SD	5.09 ± 0.92	
Median (IQR)	5.10 (4.65 -5.70)	
Health Assessment Questionnaire (HAQ)		
Mild to Moderate (>1)	4	4.0
Moderate to Severe (>1-2)	69	69.0
Severe to very Severe (>2-3)	27	27.0
Min-Max	1.0-2.90	
Mean ± SD	1.82 ± 0.49	
Median (IQR)	1.73 (1.50 -2.10)	
Mobility Assessment using the Timed (sec)		
No risk of falling (<12)	56	56.0
Risk of falling (>12)	44	44.0
Min-Max	7.0-60.0	
Mean ± SD	13.12 ± 7.29	
Median (IQR)	12.0 (10.0 -14.0)	
Mini Mental State Examination (MMSE)		
Questionably Significant (26 -30)	49	49.0
Mild (21-25)	40	40.0
Moderate (10-20)	11	11.0
Min-Max	18.0-30.0	
Mean ± SD	25.8 ± 2,97	
Median (IQR)	25.0 (23.0 -27.50)	
Geriatric Depression Scale (GDS- 15)		
Score < 5	16	16.0
Suggestive depression > 5	24	24.0
Indicative of depression > 10	20	20.0
Min-Max	1.0-15.0	
Mean ± SD	7.93 ± 2.84	
Median (IQR)	8.0 (6.0 -10.0)	
Frailty Index Measurement		
No Frailty 0	10	10.0
Frailty Risk 1-3	57	57.0
Frailty ≥ 4	33	33.0
Min-Max	0.0-9.0	
Mean ± SD	3.03 ± 2.09	
Median (IQR)	3.0 (2.0 - 4.0)	

SD : Standard deviation **IQR: Inter quartile range**

Table (IV): Descriptive analysis of the studied cases according to Laboratory Investigations

	Min. – Max.	Mean ± SD.	Median (IQR)-90-
ESR	16.0 – 140.0	57.53 ± 36.93	36.0 (25.0 – 91.50)
CRP	1.0 – 49.0	11.05 ± 11.76	6.0 (3.60 – 14.0)
FBS (mg/dl)	76.0 – 192.0	103.04 ± 24.79	94.0 (89.0 – 109.0)
2h PP	94.0 – 340.0	141.95 ± 57.89	120.0 (109.0 – 135.5)
Urea (mg/dl)	20.0 - 75.0	31.91 ± 9.85	29.0 (26.0 - 33.50)
Creatinine (mg/dl)	0.69 -2.10	1.0 ± 0.30	0,90 (0.81 -1.10)
ALT (U/L)	16.0 - 38.0	27.18 ± 4-11	27,0 (24.0 - 30.0)
AST (U/L)	20.0- 39.0	28.22 ± .4.08	28.0 (25.5 - 31.0)
Albumin (gm/dl)	3.50 - 4.80	4.04 ± 0.29	4.0 (3.80- 4.20)
Triglycerides (mg/dl)	85.0 - 246.0	126.79 ± 32.78	119.0 (104.5 -135.5)
Cholesterol (mg/dl)	140.0 - 310.0	187.0 ± 36.28	180.0 (161.5 -195.0)
LDL (mg /dl)	50.0 - 160.0	106.44 ± 28.51	102 (84.0 - 131.5)
HDL (mg /dl)	34.0 - 73.0	55.99 ± 8.80	55.0 (51.50 - 61.50)
SBP (mm Hg)	90.0- 174.0	127.42±18-31	129.5 (113.0 - 140.0)
DBP (mm Hg)	53.0- 701,0	93.52± 88.20	80.0 (70.0 - 90.0)

SD: **Standard deviation** IQR: **Inter quartile range**

Table (V): Descriptive analysis of the studied cases according to RF, ANA and Anti-CCP Ab

	Min. – Max.	Mean ± SD.	Median (IQR)
RF	8.0 - 445.0	57,02 ± 66.71	44.0 (24.50 - 66.0)
ANA	0.05 -10.0	5.74 ± 7.31	1.55 (0.53 -8.95)
Anti-CCP Abs	13.0 -1118.0	300.13 ± 236.07	236.0(115.0-451.5)

SD: **Standard deviation** IQR: **Inter quartile range**

Table (VI): Relation between A questionnaire for health assessment and Mobility assessment using the timed (sec).

Mobility assessment using the timed (sec)	A questionnaire for health assessment						Test of Sig.	P
	Mild to moderate (0-1) (n= 4)		Moderate to severe (>1-2) (n= 69)		Severe to very severe (>2-3) (n= 27)			
	No.	%	No.	%	No.	%		
No risk of falling (<12)	2	50.0	44	63.8	10	37.0	χ^2= 5.734*	^{MC}p= 0.042*
Risk of falling (>12)	2	50.0	25	36.2	17	63.0		
Min. – Max.	10.0 – 13.0		7.0 – 18.0		10.0 – 60.0		H= 14.239*	0.001*
Mean ± SD.	12.0 ± 1.41		11.52 ± 2.56		17.37 ± 12.63			
Median	12.50		11.0		14.0			

MC: **Monte Carlo** H: H for **Kruskal Wallis test** χ^2: **Chi square test**

p: p value for comparison between the studied categories *: Statistically significant at p ≤ 0.05

Table (VII): Relation between A questionnaire for health assessment and mini mental state examination (MMSE)

Mini mental state examination (MMSE)	A questionnaire for health assessment						Test of Sig.	p
	Mild to moderate (0-1) (n= 4)		Moderate to severe (>1-2) (n= 69)		Severe to very severe (>2-3) (n= 27)			
	No.	%	No.	%	No.	%		
Questionably (10 - 20)	1	25.0	30	43.5	18	66.7	χ^2= 5.597	^{MC}p= 0.206
Mild (21 - 25)	3	75.0	30	43.5	7	25.9		
Moderate (26 -30)	0	0.0	9	13.0	2	7.4		
Min. – Max.	22.0 – 26.0		18.0 – 30.0		19.0 – 30.0		F=1.724	0.184
Mean ± SD.	24.25 ± 1.71		24.78 ± 3.02		25.96 ± 2.86			
Median	24.50		25.0		26.0			

MC: **Monte Carlo** **F**: **F for One way ANOVA test** χ^2: **Chi square test**
p: p value for comparison between the studied categories

Table(VIII): Relation between questionnaire for health assessment and geriatric depression scale(GDS-15)

Geriatric depression scale (GDS-15)	A questionnaire for health assessment						Test of Sig.	P
	Mild to moderate (0-1) (n= 4)		Moderate to severe (>1-2) (n= 69)		Severe to very severe (>2-3) (n= 27)			
	No.	%	No.	%	No.	%		
Suggest <5	1	25.0	11	15.9	4	14.8	χ^2= 9.737*	^{MC}p= 0.027*
Depression >5	3	75.0	49	71.0	12	44.4		
Indicative >10	0	0.0	9	13.0	11	40.7		
Min. – Max.	5.0 – 9.0		1.0 – 15.0		4.0 – 13.0		F=2.522	0.086
Mean ± SD.	6.75 ± 1.71		7.61 ± 2.78		8.93 ± 2.95			
Median	6.50		8.0		10.0			

MC: **Monte Carlo** **F**: **F for One way ANOVA test** χ^2: **Chi square test**
p: p value for comparison between the studied categories
*: Statistically significant at p ≤ 0.05

Table (IX): Relation between A questionnaire for health assessment and frailty index measurement

Frailty index measurement	A questionnaire for health assessment						Test of Sig.	P
	Mild to moderate (0-1) (n= 4)		Moderate to severe (>1-2) (n= 69)		Severe to very severe (>2-3) (n= 27)			
	No.	%	No.	%	No.	%		
No frailty 0	0	0.0	6	8.7	4	14.8	χ^2= 18.903*	^{MC}p= 0.001*
Frailty risk 1-3	3	75.0	48	69.6	6	22.2		
Frailty ≥ 4	1	25.0	15	21.7	17	63.0		
Min. – Max.	2.0 – 5.0		0.0 – 7.0		0.0 – 9.0		H=7.826*	0.020*
Mean ± SD.	3.0 ± 1.41		2.61 ± 1.64		4.11 ± 2.76			
Median	2.50		3.0		4.0			

MC: **Monte Carlo** H: H for **Kruskal Wallis test** χ^2: **Chi square test**
p: p value for comparison between the studied categories

Discussion:

Musculoskeletal disorders are common problems affecting the elderly [32] Increasing age, musculoskeletal tissues show increased bone fragility, loss of cartilage resilience, reduced ligament elasticity, loss of muscular strength, and fat redistribution decreasing the ability of the tissues to carry out their normal functions. [33] The loss of mobility and physical

independence resulting from arthropathies that can be particularly devastating in this population, not just physically and psychologically, but also in terms of increasing comorbidities. [34] The aim of the study was to assess the prevalence of geriatric health problems in elderly patients with common rheumatic and musculoskeletal diseases, to determine the association between health problems and quality of life through comprehensive geriatric assessment and their association with disease comorbidity One hundred elderly men and women ≥ 65 years of age, with rheumatic and musculoskeletal conditions recruited from the geriatric outpatient clinics were included in this cross sectional study. A questionnaire was used to assess functional disability, quality of life, visual analogue scale (VAS) for spinal pain, joint pain, global status, fatigue, duration of morning stiffness, review of the systems, falls and cardiovascular risks. Monitoring of comorbidities and risk factors as cardiovascular disease by blood pressure measurement, blood glucose, lipid profile, kidney and liver function assessment was performed. Monitoring for infections including hepatitis B, and C was done. Opthalmological examination, echocardiogram and X-ray of the affected joints was carried out for all elderly patients with rheumatic musculoskeletal disease.

Arthritis is a disease of articular joints that alters the joints biochemically, structurally, and physiologically. The common musculoskeletal disorder affecting the elderly population is osteoarthritis (OA). [35] This historical categorization has continuously been challenged by our continued understanding of this widespread disease. [36] Therefore, multiple descriptive categories have been proposed for local or generalized joint involvement, clinical, biochemical, and radiological presentations. [37] Ageing is associated with a state of chronic low-grade inflammation known as inflamm-ageing. Osteoarthritis is the commonest musculoskeletal disease and the main risk factor for OA is age. Rheumatoid arthritis (RA) is the second most common rheumatic disease occurring in the elderly. [38] The elderly RA population is expanding due to both increased life expectancy and an increased incidence of elderly onset RA. Elderly onset RA seems to have a characteristic clinical pattern and perhaps biological profile different to that of early onset RA. [39]

Our results demonstrated that there was a marked increase in the number of the adverse outcomes scores among the elderly such pain scale , mobility disorders, increased risk of falls, fractures, impaired ability or disability to perform activities of daily living, risk of malnutrition, geriatric depression risk, frailty risk , urinary incontinence , sleep disturbance, increased duration of mourning stiffness , mobility risk, and increased risk of cardiovascular comorbidities as elevated blood pressure , kidney functions , liver functions impairment , elevated ESR, CRP, ANA, RF, Anti-CCP, FBS, 2hPP, serum uric acid , elevated blood pressure and lipid profile.

Biochemical and mechanical changes associated with aging are the greatest non-modifiable risk factors for osteoarthritis development and progression. [40] Women have a higher prevalence and severity of osteoarthritis, especially in the hands, hips, and knees. However, results suggesting that estrogen plays a role in incidence and progression have been conflicting. [41,42] Multiple osteoarthritis genetic loci on genome-wide scans have been identified that may help to elucidate the pathophysiology and associated phenotypes in the future. [43] Osteoarthritis starts as a biochemical process affecting the synovium, cartilage, or subchondral bone and progresses to biochemical and anatomical abnormalities of the entire joint complex. The initial phases of this biochemical process consist of joint inflammation, as documented by Driban et al. [44] through synovial fluid protein concentration analysis Trauma, whether related to a major joint injury or occupational microtrauma, destabilizes and deforms the joint, worsening the mechanical forces affecting the cartilage and subchondral bone. [45] Ligament laxity, sarcopenia related to quadriceps weakness in knee osteoarthritis, and

osteoporosis also contribute to the progression of osteoarthritis among elderly population. (46) The synovium can be the source of multiple pro-inflammatory mediators that lead to pain and changes to the synovial fluid. The synovial fluid nourishes the avascular, aneural cartilage as well as produces hyaluronic acid and lubricin to reduce friction during movement. An increase in pro-inflammatory and catabolic products decrease the concentrations of cartilage-protecting factors and increase the production of cartilage degradation factors. There are also changes to the molecular weight of hyalouronic acid and decrease the concentration of lubricin. (47) Early osteoarthritis bone remodeling could occur through different mechanisms: cellular signaling leading to bone remodeling and resorption and vascular invasion leading to cartilage degeneration and diminished mechanical integrity. When an imbalance exists in the structure or functioning of the extracellular matrix of the cartilage, additional inflammatory mediators and mechanical stress create a "vicious cycle" of cartilage degeneration. This change leads to multiple molecular events and consequences including altered gene expression related to senescence, DNA and telomere dysfunction, altered protein secretion, oxidative damage, decreased growth factor response, and apoptosis, precipitating cartilage destruction and susceptibility for osteoarthritis in the elderly. (48)

Villa-Blanco JI et al **(49)** documented that elderly onset rheumatoid arthritis is usually defined as rheumatoid arthritis onset after 65 years of age. This specific rheumatoid arthritis classification has a prevalence of around 2% and accounts for between 10% and 33% of all rheumatoid arthritis cases.

Tutuncu Z et al **(50)** documented that disease activity is significant in elderly onset rheumatoid arthritis, including higher swollen and tender joint counts, a longer duration of morning stiffness, and greater alterations in quality-of-life indices. In 25% of elderly onset rheumatoid arthritis patients, the initial involvement of the proximal limb joints was observed elderly onset rheumatoid arthritis patients.

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Conclusion:

Aging population has become one of the most dramatic and influential developments in the 20th century. Musculoskeletal disorders are debilitating conditions that significantly impair the state of health, especially in elderly people with musculoskeletal disorders. Comprehensive geriatric assessment is an essential tool in diagnosis and treatment plan in geriatric musculoskeletal diseases, thus could improve patient management and satisfaction. Geriatric patients with chronic pain should be examined and investigated for musculoskeletal diseases.

Conflicts of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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