

*Research Article***Calprotectin as biomarker in diabetic patients with peripheral neuropathy****Noussa M. El-adawy, Sahar H. El-Hini, Enas M. Hassan and Eman A. Abd El wahab**

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Abstract

Introduction: Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia associated with symptoms like polydipsia, polyphagia, polyuria, blindness, weight loss or gain, sore heals, burning and tingling sensation. **Aim of the work:** This study aimed to evaluate serum calprotectin level as pro-inflammatory biomarker for incidence of neuropathy in recently discovered diabetic and pre diabetic patients in Egyptian subjects. **Subjects and Methods:** This study was conducted on 60 persons (40 Patients and 20 controls) patients were selected from our diabetic outpatient clinic of internal medicine department at Minia University hospital. **Results:** The calprotectin was significantly higher in the diabetic than the control group ($p < 0.001$). The TC (209.9 ± 60.6), LDL (145.4 ± 41.7) and triglycerides (165.4 ± 57.7) were significantly higher in diabetic patients than the control group with ($p < 0.05$, $p < 0.004$ LDL & $p < 0.001$) respectively. **Conclusion:** Diabetic peripheral Neuropathy (DPN) is the most common and earliest complication of diabetes. Serum calprotectin was elevated in diabetic peripheral Neuropathy .

keywords: Calprotectin, Diabetic Peripheral Neuropathy, Nerve Conduction study

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia associated with symptoms like polydipsia, polyphagia, polyuria, blindness, weight loss or gain, sore heals, burning and tingling sensation (Sandireddy et al., 2014).

Diabetes mellitus has attained epidemic proportions worldwide. in 2017 the International Diabetes Federation (IDF) estimated that 425 million people(aged 20-79) with diabetes in the world. That number is projected to rise to 629 million by 2045. The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM (IDF, 2017).

Diabetes is associated with both macrovascular and microvascular complications, in which the major microvascular complication is diabetic neuropathy (DN) with a prevalence of 50-60% (Sekimoto et al., 2012).

The neuropathy progresses with decreasing nerve functionality and nerve blood perfusion which may result in malnourished nerve and

leads to permanent nerve damage. The clinical manifestations of diabetic neuropathy include numbness, burning, tingling sensation and intractable pain (Peng et al., 2011). Calprotectin (myeloid related protein 8/14) belong to S100 protein family composed of two calcium binding cytoplasmic calgranulins which are expressed in activated human granulocyte and macrophages in inflammatory conditions among its functions are activation of NADPH oxidase, toll like receptors4 (TLR4), and advanced Glycation end products (AGES) which are important in signaling pathways in pathogenesis of micro and macrovascular complications of diabetes (Peng et al., 2011).

Aim of the work

This study aimed to evaluate serum calprotectin level as pro-inflammatory biomarker for incidence of neuropathy in recently discovered diabetic and pre diabetic patients in Egyptian subjects.

Subjects and Methods

This study was conducted on 60 persons (40 Patients and 20 controls) patients were selected from our diabetic outpatient clinic of internal

medicine department at Minia University hospital according to criteria of American diabetic association (2017) for diabetes.

All subjects were divided into three groups:

Group I (diabetic) patients: Which includes 20 patients newly diagnosed.

Group II (Pre-diabetic) patients : Which includes 20 patients.

Group III (control group) Also, this study included 20 healthy subjects.

Exclusion criteria:

Subjects had infectious diseases, inflammatory diseases, liver failure, malignancies, neurodegenerative diseases, renal failure, cerebrovascular diseases, medical history of serious trauma to the limbs, use of neurotoxic medication, as excessive alcohol consumption and smokers were excluded from the study both in study and control groups.

Clinical Study:

All groups were subjected to full history taking and thorough clinical examination. Diabetic group had to be diagnosed type 2 diabetics with duration of known diabetes less than 1 year.

Clinical assessment of neuropathy:

All cases (n=60) were subjected to a detailed neurological assessment looking for symptoms and signs of peripheral neuropathy (PN) and then to grade it according to the scores. All persons were subjected to nerve conduction.

Laboratory investigations:

- a) Serum Calprotectin
- b) Lipid profile
- c) Liver function tests
- d) Renal function tests
- e) HB A1C
- f) Fasting blood glucose
- g) 2h post prandial blood glucose.

Results

Comparison of calprotectin, lipid profile parameters between the studied groups.

	Group I Diabetic (n=20)	Group II Pre-diabetic (n=20)	Group III Control (n=20)	P - value		
Calprotectin ng/ml				<0.001*		
Range	(71-2112)	(76-880)	(59-183)	I vs II	I vs III	II vs III
Mean ± SD	689.2±446.7	426.3±269.8	99.1±34.3	0.04*	<0.001*	<0.001*
Median	748	417	87			
TC mg/dl				0.089		
Range	(81-364)	(142-261)	(123-197)	I vs II	I vs III	II vs III
Mean ± SD	209.9±60.6	199.1±38.5	176.8±40.2	0.757	0.05*	0.05*
HDL mg/dl				0.880		
Range	(25-58)	(25-57)	(29-45)	I vs II	I vs III	II vs III
Mean ± SD	36±8.5	35.7±8.4	34.9±4.4	0.988	0.874	0.937
LDL mg/dl				0.006*		
Range	(39-237)	(65-194)	(60-138)	I vs II	I vs III	II vs III
Mean ± SD	145.4±41.7	127.8±33.9	110.4±19.1	0.218	0.004*	0.061
TG mg/dl				0.001*		
Range	(101-295)	(59-260)	(32-147)	I vs II	I vs III	II vs III
Mean ± SD	165±57.7	147.4±53.8	101.6±36.9	0.512	0.001*	0.015*

The pre diabetics showed higher significant difference of the Calprotectin , total cholesterol and triglyceride than the control subjects . Moreover, the calprotectin was significantly lower in pre diabetics than the diabetics. The calprotectin was significantly higher in the diabetic than the control group. The TC and triglycerides were significantly higher in diabetic patients than the control group.

Discussion

In this study we aimed to investigate the possible associations between (serum calprotectin) (as pro-inflammatory) and peripheral neuropathy in pre diabetics or type 2DM patients. DPN is the most common and earliest complication of diabetes that was found to affect 33.5% of patients with T2DM at multiple hospitals across Korea (n=3,999), compared with retinopathy (21.0%) and nephropathy (15.7%) (Won et al., 2012). It was believed that activation of inflammatory cascade, pro-inflammatory cytokine up regulation, and neuroimmune communication pathways are important in structural and functional nerve damage, which caused development of diabetic peripheral neuropathy (Striz & Trebichayský, 2004).

Calprotectin is critically involved in pro-inflammatory signaling (Pruenster et al., 2016). It is proposed that calprotectin complex is a biomarker for inflammation and is beneficial in monitoring disease activity. High levels of calprotectin levels are reported in chronic inflammatory diseases such as rheumatoid arthritis, allograft rejection, inflammatory bowel disease, cancer, pulmonary disease, obesity, atherosclerosis (Striz I, Trebichayský, 2004 , Mortensen et al., 2009 and Catalan et al., 2011)

Conclusion and Recommendation

In this study, we had revealed that level of serum calprotectin significantly elevated in hyper glycaemic patients with peripheral neuropathy. suggesting that this molecule may have a role in pathogenesis of neuroinflammation among these patients. The proinflammatory stage seems to begin from the very early preclinical stages, and pre diabetic patients are at risk of developing diabetic neuropathy even before progression to type 2 Diabetes. Serum calprotectin levels in the future may be used as potential markers of its presence, severity and progression of the diabetic peripheral neuropathy. Therapeutic strategies for blocking S100A9 and its activity are recently under development in inflammatory diseases. We recommend using of Michigan Neuropathy Screening Instrument (MNSI) and Nerve

conduction study for prompt detection of Diabetic neuropathy. Nerve Conduction Study (NCS) is a more reliable tool for detection of diabetic sensorimotor polyneuropathy especially for the sub-clinical neuropathies. Routine NCS should be done on diabetics at least on yearly basis for diabetic and pre diabetic patients.

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