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INFLAMMATORY MARKERS AND RISK OF DEVELOPING MUSCULOSKELETAL DISORDER IN TYPE 2 DIABETIC PATIENTS

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Abstract

Background: Diabetes may affect the musculoskeletal system in a variety of ways. The metabolic perturbations in diabetes (including glycosylation and collagen accumulation in periarticular structures) result in changes in the connective tissue leading to diffused fibro-arthrosis. As a result patient is debilitated by cheiroarthropathy, dupuytren contracture, frozen shoulder and trigger finger etc. The immunological parameter like tumor necrosis factor-α and interleukin-6 in type 2 diabetes also play an important role in musculoskeletal disorders. The aim of this study was to estimate the biochemical and immunological parameters in diabetic subjects suffering from musculoskeletal disorders.

Methods: This study has been conducted on 150 subjects, out of whom 50 were diabetic with musculoskeletal disorders, 50 age matched diabetic controls without musculoskeletal disorders and 50 healthy controls. HbA_{1C} level was evaluated by the method of Rai B. and Pattabiraman. Fasting blood sugar and lipid profile levels were evaluated by fully automated Biosystem A-25 autoanalyser (Biosystem, Barcelona, Spain). TNF-α and IL-6 was estimated by highly sensitive SANDWITCH ELISA using their respective kits (ELISA Reader: Rayto Life and Analytical Sciences Co. Ltd., CHINA; Kits: IMMUNOTECH, A Backman Coulter Company, FRANCE), according to manufacturer instructions. Data analyses were performed with the Statistical Package for the Social Sciences (SPSS® version 16.0; SPSS Inc., Chicago, IL, USA).

Results: The serum level of TNF-α, IL-6, FBS, HbA_1c and lipid profile except HDL have shows significant increase ($p<0.05$) in both diabetic with MSDs and diabetic without MSDs groups as compared to control groups. TNF-α, IL-6, FBS, HbA_1c and lipid profile except HDL have shows significantly higher level ($p<0.01$) in diabetic subject with musculoskeletal disorders as compare to diabetics without musculoskeletal disorders.

Conclusion: From the above study it is concluded that chronic hyperglycemia increases circulating cytokines concentrations, contributing to musculoskeletal disorder.

Key words: musculoskeletal disorder; tumor necrosis factor-α; interleukin-6; glycosylated hemoglobin.

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Introduction:

Diabetes mellitus is multi system disease characterized by persistent hyperglycemia that has both acute and chronic biochemical and anatomical squeal, may cause irreversible damage to many organs and organ systems [1]. This disease affects connective tissues in many ways and causes different alterations in periarticular & musculoskeletal system [2.] Although the exact etiology of diabetes associated musculoskeletal disorders remain unclear, but there is clear evidence that hyperglycemia may accelerate non enzymatic glycosylation and abnormal collagen deposition in particular connective tissues, which alter the structural matrix and mechanical properties of these tissues leading to diffused fibro-orthrosis [3,4]. As a result patient's quality of life may change.

''Musculoskeletal disorders'' include a wide range of inflammatory and degenerative conditions affecting the muscles, tendons, ligaments, joints, peripheral nerves and supporting blood vessels. These include clinical syndromes such as tendon inflammations and related conditions (tenosynovitis, cheiroarthopathy, dupuytren contracture, frozen shoulder etc.) [5].

The high serum concentration of these inflammatory markers such as proinflammatory cytokines is also associated with severity of early onset of MSDs [6]. Cytokines are the chief stimulators of acute phase response proteins and contribute to the development and remediation of signs and symptoms of acute and chronic inflammation[7].Diabetes mellitus is therefore also considered as a chronic inflammatory disease[8]. Proinflammatory cytokines activates signaling cascade including nuclear factor of κB (NFκB) and c-Jun NH2-Terminal kinase (JNK) which inhibit insulin signaling by phosphorylation of insulin receptor substrate -1(IRS-1) and IRS-2, thereby inhibiting insulin signaling and stimulation of expression of suppressor of cytokines signaling proteins, which bind IRS-1 and IRS-2 and mediate their degradation [9.]

Low grade inflammation is a part of widespread activation of the innate immune system, which plays a crucial role in the pathophysiology of type 2 diabetes and associated complication such as MSDs[10]. In support of this increased serum level of IL-6 and TNF-α are associated with increased risk of musculoskeletal disorder in type 2 diabetes and insulin resistance [11]. Hence the study has been planned to know the status of inflammatory markers associated with MSDs in type 2 diabetes mellitus.

Material & Method:

The present study was carried out in Department of Biochemistry in collaboration with Department of Orthopedics, J.A. Groups of Hospitals and G.R. Medical College, Gwalior (M.P.). The study protocol was approved by Institute Ethical Committee and written consent also been taken from patients before starting the work. The control group included 50 healthy individual, 50 were diabetic with musculoskeletal disorders and 50 age matched diabetic controls without musculoskeletal disorders of both the sex were taken. All diabetic patients were on medication with oral hypoglycaemic drugs like sulphonylureas or metformin.

Inclusive criteria: Diabetic patients with MSDs and age related disorders like hypertension, blood pressure should within normal range with medication.

Exclusion criteria: History of other inflammatory disease (e.g. lupus, rheumatoid arthritis and hypertension), cancer, known coronary artery disease, disease processes that required ongoing treatment with steroids or NSAIDs (non-steroidal anti-inflammatory drugs) and chronic cigarette smoking. 10 ml of blood sample was withdrawn from the anticubital vein following overnight fasting. The blood sample was collected in plain and sodium citrate vacutainers. Serum was separated from blood sample for all the biochemical and immunological investigations excluding HbA1C. HbA1C was estimated in haemolysate by the method of Rai B. and Pattabiraman (1984)[12]. Fasting blood sugar and lipid profile levels were evaluated by fully automated Biosystem A-25 autoanalyser (Biosystem, Barcelona, Spain). TNF-α and IL-6 was estimated by highly sensitive SANDWITCH ELISA using their respective kits (ELISA Reader: Rayto Life and Analytical Sciences Co. Ltd., CHINA; Kits: IMMUNOTECH, A

Backman Coulter Company, FRANCE), according to manufacturer instructions.

Statistical analysis

Differences between continuous variables were tested with analyses of variance (one-way ANOVA) utilizing Dunnet T3 test. One Way ANOVA was used to estimate differences between ages matched controls, type 2 diabetes mellitus without musculoskeletal complication and in type 2 diabetes mellitus with musculoskeletal disorders. The Pearson's correlation coefficient test was performed to determine correlation among risk factors. Data analyses were performed with the Statistical Package for the Social Sciences (SPSS® version 16.0; SPSS Inc., Chicago, IL, USA).

Results:

Type 2 diabetes mellitus group with MSDs consisted of 50 patients (25 males and 25 females), diabetic without MSDs consisted 50 patients (24 males and 26 females) and control group consisted of 50 age and sex matched subjects (24 males and 26 females). Demographic data for the three groups are shown in Table 1. Table 2 shows the comparison of biochemical and immunological parameters of healthy control with diabetic without MSDs and diabetic with MSDs. FBS, HbA1C and inflammatory markers are highly significant (P>0.01), TC, TG and LDL are significantly higher (P>0.05) while HDL is significantly lower (P>0.05) in patients with diabetic without MSDs as compared to controls. FBS, HbA1c, TNF-α, IL-6, TC, TG, LDL and VLDL are highly significant (P>0.01) while HDL is highly significantly lower (P>0.01) in diabetic with MSDs as compared to controls. Table 3 shows all the biochemical and immunological parameters is highly significant (P>0.01) except HDL in diabetic with MSDs patients as compared to diabetic without MSDs.

Moderate, though significant correlations were found between age and type 2 diabetes duration (P>0.001), age and HbA1C (P>0.002), HbA1C and type 2 diabetes duration (P>0.027), HbA1C and TNF-α (P>0.037), HbA1C and IL-6 (P>0.045) (Table 4).

Discussion:

Diabetes mellitus is a metabolic disorder of multiple etiology with full range of complications starting from brain and going down to feet and toes with involvement of whole body organ and musculoskeletal system (skin, muscle, bone, tendon and joints). Therefore this fact cannot be over-looked that diabetes mellitus is a difficult to understand and even much difficult to handle problem. It provides a basic platform for thought to every aspects of medical science. This particular study is a humble attempt to unravel the inflammatory basis of musculoskeletal aspects of diabetes mellitus. Following reasons in particular made us to look quickly and furtively into this alley of this disease:

Musculoskeletal disorders are age related disorders generally manifested at the age of 45 years onward. Therefore diabetic subjects are always in dilemma that whether these disorders are due to diabetes or advancing age, although these are the major cause of morbidity to these patients.

The available research data and literature till date are not sufficient to throw the light on inflammatory basis of musculoskeletal disorders in diabetes.

Therefore we conducted this study to know whether a relationship exists between biochemical and immunological parameters with severity and early onset of musculoskeletal disorders in type 2 diabetic patients.

In our study we find out that the onset of MSDs in type 2 diabetes mellitus appears with the duration of 12 and 11 years (Table No. 1) in male and female respectively with inconsistent sugar level. The higher BMI has consistently been associated with increased risk for type 2 diabetes [13,14]. Overweight and obesity in middle aged men and women with metabolic syndrome are associated with complications of diabetes[15]. In our study we found significant increase of BMI in group III subjects as compared to group I and group II subjects in both sex (Table No. 1).

Type 2 diabetes mellitus is a heterogeneous condition characterized by the presence of both impaired insulin secretion and insulin resistance. Hyperglycemia plays an important role in chronic complications of diabetes and is postulated to be

associated with increased formation of advanced glycation end products. In our study, we found highly significant increase of FBS and HbA1C ($p<0.01$) in group II and group III diabetic subjects as compared to group I subjects in both sex (Table No. 2). The increase in HbA1C in group II and group III diabetic subjects is due to high concentration of glucose present in both inside and outside the cell, favoring the occurrence of spontaneous and non enzymatic reactions between glucose and protein in intra and extracellular compartments resulting in advanced glycation end products in type 2 diabetes mellitus subjects[16]. Furthermore AGEs bind to specific receptors on endothelial cells causing vascular permeability, procoagulant activity, adhesion molecule expression and monocytes influx in the cell contributing vascular injury in type 2 diabetes mellitus. The protein modification and vascular changes are due to high HbA1C formation which is magnified by ambient glucose concentration in type 2 diabetes mellitus subjects[17-19].

The other parameters like lipid profile and cytokines in diabetic male and female subjects of group II and group III as compared to group I showed same pattern of change i.e. the significant increased ($p<0.01$, $p<0.05$) of TG, TC, LDL and VLDL with significant decrease in HDL and significant increase ($p<0.01$) of inflammatory cytokines TNF-α and IL-6 (Table No. 2). These findings are consistent with Verma M et al, 2006; Smith S et al, 2008; Al-Dhar MHS et al, 2010.[20-22]

Previous studies noted that hypercholesterolemia may also be associated with crystal arthopathy due to presence of crystalline cholesterol in joints [23]. Sanderson et al, 1992 [24] reported relationship of serum lipid and lesions in hand of diabetic patients. The dupuytren's patients with diabetes mellitus showed significant high cholesterol and triglycerides. Salek AHM et al, 2010 [25] reported that hypertriglycerdemia may be associated with frozen shoulder of diabetic patients, may be due to hyperglycemia and increased HbA1C level (Leading to formation of AGEs) as compared to diabetic without MSDs (Table 3).

Musculoskeletal disorders are related to inflammatory process. Though the etiology is unclear but reported studies show the increased serum cytokines are part of process. Cytokines and other growth factors facilitate tissue repair and remodeling as a part of inflammatory process. Their increased levels are also reported in frozen shoulder[26,27].

The biochemical mechanisms of tendon degeneration are similar in aging and diabetes. The most important abnormality is non enzymatic glycosylation of collagen with advanced glycation end products formation (AGEs). These AGEs affects physical and chemical properties of protein increasing the amount of intra-molecular collagen-cross links, resulting in decrease elasticity of muscle and is more likely to tear. These AGEs could affects this process through specific receptors (RAGE) which are present on condrocytes, tenocytes and fibroblast. Binding of these receptors-specific signaling takes place resulting in enhanced generation of reactive oxygen species (ROS) and activation of NF-κB. In diabetes RAGE, vasculoendothelial growth factors and cytokines (TNF-α and IL-6) are over expressed and it may explain why diabetic show increased prevalence of lesions and inflammatory reaction [28.]

In our study when we compared the results of group III subjects with group II controls, we observed increased levels of TNF-α and IL-6 (Table No. 3). The release of these inflammatory markers was more significant in group III subjects of both sex may be due to overexpression of TNF-α is associated with long standing of disease [29]. TNF-α is the first cytokine recognized to have a direct role in promoting insulin resistance in MSDs[30]. del Aguila LF et al, 1999 [31] demonstrated that TNF-α decreases tyrosine phosphorylation of IRS-1 and increases IRS-1 serine phosphorylation. This relative increase in serine to tyrosine phosphorylation may lead to increased ubiquinization/ proteosomal degradation of IRS-1 leading to decreased insulin metabolic signaling. Furthermore, TNF-α diminishes skeletal muscle IRS tyrosine phosphorylation and Akt activation in a p38 through MAP kinase-dependent pathway [32]. TNF-α stimulates the production of diacylglycerol and ceramide, which are associated with impaired insulin sensitivity both in vitro and in vivo [33].

A close relationship between chronic inflammation and MSDs has been supported by infiltration of inflammatory cells into skeletal muscle, as evidenced by increased macrophages and CD154 levels in muscle biopsies from type 2 diabetes mellitus patients [34]; increased inflammatory molecule levels, including TNF-α, IL-6, inducible nitric oxide synthase, fibrinogen, C-reactive protein (CRP), plasminogen activator inhibitor-1 and sialic acid in skeletal muscle [35]; increased circulating inflammatory cytokines originating from adipose tissue such as TNF-α, IL-6; skeletal muscles, per se, generate and secrete several inflammatory cytokines [36]. Kim HJ et al, 2004 [37] investigated that circulating level of IL-6 is elevated in various insulin-resistant states, including type 2 diabetes mellitus. In vivo, acute IL-6 treatment in mice reduces insulin-stimulated skeletal muscle glucose uptake associated with defects in IRS-1/PI 3-kinase activity and increases in fatty acyl-CoA levels in skeletal muscle. IL-6 has inhibitory effects on the gene transcription of IRS-1, GLUT-4 and peroxisome proliferator-activated receptor-γ (PPAR-γ) under these conditions[38]. Moreover, IL-6 induces a rapid recruitment of IRS-1 to the IL-6 receptor complex in cultured skeletal muscle cells and induces a rapid and transient IRS-1 serine phosphorylation and resultant increased IRS-1 ubiquinization in skeletal muscle tissue [39].

Correlative studies showed the association between different parameters in our study like, duration of disease in uncontrolled diabetics is closely associated with onset of musculoskeletal disorders. We found positive correlation values between duration of disease and musculoskeletal disorders (Table No. 4). This is consistent with the observation of Crispin JC et al, 2003; Ardic F et al, 2003; Arkkila PET, 2003; Brown MA, 2005; Ryzewicz et al, 2006; Douloumpakas I et al, 2007; Geraci A et al, 20111,[40-45].

The positive correlation was present between age of diabetic subjects with duration of disease and HbA1C level in diabetic suffering from MSDs (Table No. 4). As the duration of disease increased the risk for cheiroarthopathy increased with age[46]. Similarly HbA1C level also increase as age advances in type 2 diabetic subjects. No significant correlation was found gender wise in diabetic subjects[47].

It is assumed that uncontrolled diabetes mellitus cause a decrease in muscle power. The underlying may be diabetic neuropathy, macro- and microangiopathy. Moreover advancing age appears to alter the physical and chemical properties of skeletal muscle proteins. Alterations include: reduced contractile, mitochondrial and enzyme protein synthesis rate, altered expression and post transcriptional modification to muscle proteins, reduced maximum voluntary muscle strength etc[48].

Persisting hyperglycemia in uncontrolled diabetics showed elevated level of inflammatory markers in our study. We found a significant positive correlation between HbA1C and inflammatory markers TNF-α and IL-6 (Table No. 4) in diabetics suffering from MSDs. Hyperglycemia induced changes in gene expression and biochemical reactions such as advanced glycation end products in long lived macromolecules may not be reversed while glycemia returns to normal level. Poor control progressively interrupted on the cell[49]. Advanced glycation end products are also known to stimulate cytokines production from macrophases and thus glycation of long lived molecules (Proteins) throughout the body may upregulate cytokines production. They also play an important role in impaired β-cell function of pancreatic cells in type 2 diabetes mellitus.

Therefore, a cascade mechanism could be explained for the onset of these disorders as: Due to persistent hyperglycemia in uncontrolled diabetes mellitus, release of inflammatory markers takes place and as the age of diabetic person and duration of disease increases leading to onset of musculoskeletal disorders.

Conclusion:

Different musculoskeletal disorders are frequently observed in long standing diabetes (After 10 years). These disorders in diabetes are closely associated with BMI. Musculoskeletal disorders are related to increase inflammatory markers along with pain i.e. adhesive capsulitis (Stiffness in shoulder), carpel tunnel syndrome, and tenosynovitis which are associated with pain not only in diabetes but in non diabetics also (Because musculoskeletal diseases

are believed to be age related in normal person also). This study also confirm the importance of studying musculoskeletal disorders in diabetics, as these are ignored and if they are not treated timely they become the major cause of crippling deformities and disabilities for diabetic patients.

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Table 1. Demographic data for diabetic subjects with and without MSDs who were assessed for biochemical and immunological parameters. Values expressed as mean±SD

S. No.	Parameters		Healthy control (n=50)	Diabetic without MSDs (n=50)	Diabetic with MSDs (n=50)
1	Age (years)	M	56.32±07.50	58.44±08.95	58.57±06.60
		F	56.04±08.11	57.24±08.27	58.67±07.24
2	Duration of diabetes (years)	M	00.00	10.24±02.31	12.05±03.36
		F	00.00	10.56±02.27	11.88±02.98
3	BMI (Kg/m2)	M	23.60 ±1.49	25.51 ± 2.43	27.94± 4.01
		F	22.00 ± 1.70	25.34± 2.32	28.60 ± 4.21

Table 2. Showing the significant changes of biochemical and immunological parameters of control with T2DM patients without MSDs and with MSDs

Groups		FBS (mg %)	HbA_{1C} (M Hexose / M Hb)	Lipid Profile					TNF-α (pg/ml)	IL-6 (pg/ml)
				TC (m g%)	TG (mg %)	HDL-C (mg %)	LDL-C (mg %)	VLDL-C (mg %)		
Healthy controls	M (n=24)	74.33 ±11.76	0.26 ±0.014	158.25 ±17.57	120.66 ±8.370	47.72 ±9.06	86.73 ±14.70	24.1 ±1.75	9.23 ±1.22	9.68 ±1.08
	F (n=26)	72.61 ±10.3	0.26 ±0.02	161.43 ±45.03	120.92 ±6.13	44.43 ±6.48	85.17 ±29.83	24.15 ±1.27	9.09 ±1.45	9.16 ±1.07
Diabetic without MSDs	M (n=24)	133.75 ±29.98**	0.58 ±0.05**	185.75 ±38.46*	151.58 ±52.13*	34.70 ±2.65*	119.87 ±41.80*	31.15 ±8.50*	13.99 ±2.39**	13.08 ±2.30**
	F (n=26)	152 ±39.53**	0.54 ±0.09**	187.69 ±32.18*	169.61 ±46.79*	35.66 ±3.07*	112.12 ±35.59*	33.92 ±9.35*	12.96 ±1.34**	12.85 ±2.30**
Diabetic with MSDs	M (n=25)	158.08 ±33.66**	0.66 ±0.10**	218.16 ±42.62**	194.64 ±57.40**	24.88 ±3.22**	154.45 ±47.46**	38.95 ±11.44**	37.71 ±17.31**	33.90 ±11.12**
	F (n=25)	176.24 ±63.50**	0.73 ±0.08**	237.8 ±41.67**	230.44 ±54.25**	25.84 ±3.48**	165.74 ±44.59**	46.08 ±10.85**	38.81 ±12.32**	30.20 ±7.58**

Values expressed as mean±SD , *($p<0.05$) Significant,**($p<0.01$)Highly Significant

Table 3. Showing biochemical and immunological parameters in type 2 diabetics without MSDs and with MSDs

Groups		FBS (mg %)	HbA1C (M Hexose / M Hb)	Lipid Profile					TNF-α (pg/ml)	IL-6 (pg/ml)
				TC (mg%)	TG (mg %)	HDL-C (mg %)	LDL-C (mg %)	VLDL-C (mg %)		
Diabetic without MSDs	M (n=24)	133.75 ±29.98	0.58 ±0.05	185.75 ±38.46	151.58 ±52.13	34.70 ±2.65	119.87 ±41.80	31.15 ±8.50	13.99 ±2.39	13.08 ±2.30
	F (n=26)	152.00 ±39.53	0.54 ±0.09	187.69 ±32.18	169.61 ±46.79	35.66 ±3.07	112.12 ±35.59	33.92 ±9.35	12.96 ±1.34	12.85 ±2.30
Diabetic with MSDs	M (n=25)	158.08 ±33.66**	0.66 ±0.10**	218.16 ±42.62**	194.64 ±57.40**	24.88 ±3.22*	154.45 ±47.46**	38.95 ±11.44**	37.71 ±17.33**	33.90 ±11.12**
	F (n=25)	176.24 ±63.50**	0.73 ±0.08**	237.8 ±41.67**	230.44 ±54.25**	25.84 ±3.48*	165.74 ±44.59**	46.08 ±10.85**	38.81 ±12.32**	30.20 ±7.58**

Values expressed as mean±SD, *($p<0.05$) Significant, **($p<0.01$)Highly Significant

Table 4. Correlation between age, duration of diabetes, musculoskeletal complication, HbA_{1C} and inflammatory markers in type 2 diabetic subjects with MSDs

S.No.	Characteristics	*r*-value	*P*-value
1	**MSDs versus type 2 diabetes mellitus duration**	0.399	0.000
2	**Age versus type 2 diabetes mellitus duration**	0.554	0.000
3	**Age versus HbA_{1C}**	0.304	0.002
4	**Type 2 diabetes mellitus duration versus HbA_{1C}**	0.193	0.027
5	**HbA_{1C} versus TNF-α**	0.209	0.037
6	**HbA_{1C} versus IL-6**	0.201	0.045

References:

1. Crispin JC, Alcocer-Varela J. Rheumatologic manifestations of diabetes mellitus. Am J Med 2003, 114: 753-757.
2. Rosenbloom AL, Silverstein JH. Connective tissue and joint disease in diabetes mellitus. Endicrinol Metab Clin North Am 1996, 25: 473-483.
3. Goldberg BA, Scarlat MM, Harryman DT 2 nd. Management of the stiff shoulder. J Orthop Sci 1999, 4: 462-671.
4. Shulte L, Roberts MS, Zimmerman C et al. A quantitative assessment of limited joint mobility in patients with diabetes. Goniometric analysis of upper extremity passive range of motion. Arthritis Rheum 1993, 36: 1429-1443.
5. National Research Council. The Institute of Medicine. Musculoskeletal disorders and the workplace: Low back and upper extremities. National Academy Press, Washington, DC 2001.
6. Stephen JC, Mary FB, Kathryn AW, Mamta AMIN, Ann EB. Inflammatory biomarkers increase with severity of upper-extremity

overuse disorders. Clinical Science 2007, 112: 305–314.
7. Ruminy P, Gangneux C, Claeyssens S, Scotte M, Daveau M, Salier JP. Gene transcription in hepatocytes during the acute phase of a systemic inflammation: from transcription factors to target organ. Inflamm Res 2001, 50: 383–390.
8. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005, 115: 1111–1119.
9. Morris MF: Insulin receptor signalling and regulation. In textbook of Diabetes. 3rd ed. Picup JC, Williams G, Eds. Oxford, U.K., Blackwell 2003, 14.1- 14.17.
10. Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia 1997, 40:1286-1292.
11. Kern PA, Ranganathan S, Li CL, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. American Journal of Physiology-Endocrinology and Metabolism 2001, 280:745-751.
12. Rai KB, Pattabiraman TN. Glycosylated haemoglobin levels in iron deficiency anaemia. Indian J Med Res 1986, 83: 234-6.
13. Vazquez G, Duval S, Jacobs DR JR, Silventoinen K. Comparision of body mass index, waist circumference and waist/hip ratio in predicting incident: a meta-analysis. Epidemiol Rev 2007, 29: 115-128.
14. Nyamdroj R, Qiao Q, Lam TH, Tuomilehto J, Ho SY, Pitkaniemi J, Nakagami T, Mohan VJanus ED, Ferreira SR. BMI compared with central obesity indication in relation to diabetes and hypertension in Asians. Obesity (Silver Spring) 2008, 16: 1622-1635.
15. Arnlov J, Sundstrom J, Ingelsson E, Lind L. Impact of BMI and the metabolic syndrome on the risk of Diabetes in middle-aged men. Diabetes Care 2011, 34: 61-65.
16. Suji G and Sivakami S. Glucose, glycation and ageing. Biogerontology 2004, 5: 365-373.
17. Sheetz MJ, King GL. Molecular understanding of hyperglycemia: adverse effects for diabetic complications. JAMA 2002, 288: 2579-2588.
18. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. Circulation 2003, 108:1527-1532.
19. Mahato RV, Gyawali P, Raut PP, Regmi P, Singh KP, Pandeya DJ, Gyawali P. Association between glyacemic control and serum lipid profile in type 2 diabetic patients: glycated haemoglobein as a dual biomarker. Biomedical Research 2011, 22(3): 375-380.
20. Verma M, Paneri S, Badi P, Raman PG. Effect of increasing duration od diabetes mellitus type 2 on glycated hemoglobin and insulin sensitivity. IJCB 2006, 21(1): 142-146.
21. Smith S and Lall AK. A study on serum lipid profile levels of diabetics and non-diabetics among naini region of Allahabad, India. Turk J Biochem 2008, 33(4): 138-141.
22. Al-Dhar MHS and Jiffery EH. Increased adipose tissue expression of TNF-α and insulin resistance in obese subjects with type 2 diabetes. World J Med Sci 2010, 5(2): 30-50.
23. Struthers GR, Scott DL, Bacon PA, Walton KW. Musculoskeletal disorders in patients with hyperlipidemia. Annals of Rheumatic Diseases 1983, 42: 519-523.
24. Sanderson PL, Morris MA, Stanley JK, Fahmy NRM. Lipids and dupuytren's disease. J Bone Joint Surg [Br] 1992, 74-B: 923-7.
25. Salek AKM, Mamun MAA, Haque MA, Mannan M, Ali E, Islam S, Rizvi AN, Chowdhury AZ, Islam J, Rahman MH, Ferdous C. Serum triglyceride level in type 2 diabetes mellitus patients with or without

Frozen shoulder. Bangladesh Med Res Counc Bull 2010, 36: 64-67.
26. Mullett H, Byrne D, Colville J. Adhesive capsulitis: human fibroblast response to shoulder joint aspirate from patients with stage II disease. J Shoulder Elbow Surg 2007, 16:290-294.
27. Kelley MJ, Mcclure PW, Leggin BG et al. Frozen Shoulder: Evidence and a Proposed Model Guiding Rehabilitation. Journal of orthopaedic & sports physical therapy 2009, 39(2): 135-148.
28. Abate M, Schiavone C, Salini V. Sonographic evaluation of the shoulder in asymptomatic elderly subjects with diabetes. BMC Musculoskelet Disord 2010, 11: 1-7.
29. Rapoport HJ, Mor A, Vardi P, Ranot Y, Winker R, Hindi A, Bistrizer T. Decrease secretion of Th2 cytokines precedes upregulation and delayed secretion of Th1 cytokines in activated peripheral blood mononuclear cells from patients with insulin dependent diabetes mellitus. J Autoimmun 1998, 11: 635-42.
30. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 1993, 259: 87–91.
31. del Aguila LF, Claffey KP, Kirwan JP. TNF-α impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells. Am J Physiol Endocrinol Metab 1999, 276: 849–855.
32. de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor-B kinase in a p38 MAPK-dependent manner. J Biol Chem 2004, 279: 17070–17078.
33. Bouzakri K and Zierath JR. MAP4K4 gene silencing in human skeletal muscle prevents TNF-alpha -induced insulin resistance. J Biol Chem 2007, 282: 7783–7789.
34. Wellen KE and Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest* 2005, **115: 1111**–1119.
35. Perreault M, Marette A. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. Nat Med 2001, 7: 1138–1143.
36. Bruunsgaard H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol 2005, 78: 819–835.
37. Kim HJ, Higashimori T, Park SY, Choi H, Dong J, Kim YJ, Noh HL, Cho YR, Cline G, Kim YB, Kim JK. Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes 2004, 53:1060 -1067.
38. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-κB. Nat Med 2005, 11: 183–190.
39. Weigert C, Hennige AM, Lehmann R, Brodbeck K, Baumgartner F, Schauble M, Haring HU, Schleicher ED. Direct cross-talk of Interleukin-6 and insulin signal transduction via insulin receptor substrate-1 in skeletal muscle cells. J Biol Chem 2006, 281: 7060–7067.
40. Ardic F, Soyupek F, Kahraman Y et al. The musculoskeletal complications seen in type-II diabetics: predominance of hand involvement. Clin Rheumatol 2003, 22: 229-233.
41. Arkkila PET. Musculoskeletal disorders in diabetes mellitus: an update. Best Practice & Research Clinical Rheumatology 2003, 17(6): 945–970.
42. Douloumpakas I, Pyrpasopolous A, Triantafyllou A, Sampanis CH, Aslanidis S. Prevalance of musculoskeletal disorders in patients with type-II diabetes mellitus: a pilot study. Hippokratia 2007, 11 (4): 216-218.
43. Brown MA. Antibody treatments of inflammatory arthritis. Curr Med Chem 2005, 12: 2943-2946.
44. Ryzewicz M, Wolf JM. Trigger Digits: Principles, Management and Complications.

The Journal of Hand Surgery 2006, 31A (1): 135-146.
45. Geraci A, Bianchi R, Sanfilippo A, D'Arienzo M. Dupuytren contracture in diabetic hand. Endocrinology Studies 2011.
46. Aydeniz A, Gursoy S, Gumey E. Which musculoskeletal complications are most frequently seen in type-II diabetes mellitus? The J Int Med Res 2008, 36 (3): 505-511.
47. Arkkila PE, Kantola IM, Viikari JS et al. Shoulder capsulitis in type I and type II diabetes patients: association with diabetic complications and related diseases. Ann Rheum Dis 1996, 55: 907-914.
48. Yarasheski KE. Managing sarcopenia with progressive resistnce exercise training. J Nutr Health Aging 2002, 6(5): 349-56.
49. Lorenzi M. Glucose toxicity in the vascular complications of diabetes: the cellular perspective. Diab Metab Rev 1992, 8: 85-103.

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