Review Article **www.ijcps.com**

International Journal of Chemical and Pharmaceutical Sciences
2014, Sep., Vol. 5 (3)

ISSN: 0976-9390
IJCPS

Inflammatory markers in diabetes mellitus: An update

[1] Arun Kumar D, [2] Revathy K and [3] Swaminathan S.

[1] Senior Lab Technologist, Department of Biochemistry, Apollo Speciality Hospital,Vanagaram, Chennai, Tamil Nadu.

[2] Junior Technical Officer, Department of Biochemistry, Apollo Speciality Hospital, Vanagaram, Chennai, Tamil Nadu.

[3] Senior Consultant & Head, Department of Biochemistry, Apollo Speciality Hospital,Vanagaram, Chennai, Tamil Nadu.

[*] **Corresponding Author:** E-Mail: glorynathan@gmail.com

ABSTRACT

It has been well known that inflammation plays a key role in the development of Type 2 Diabetes Mellitus. Anti-inflammatory diet and exercise are recommended to control it. The inflammatory chemicals cytokines play a major role in Diabetes Mellitus. A host of inflammatory markers have been identified and found to influence Type 2 Diabetes, some of which are C-reactive proteins, Tumor necrosis factor, interlukin-6, serum amyloid A and fibrinogen. Number of other inflammatory markers have been recently identified, all of which are linked to Type 2 Diabetes Mellitus. This review article gives up-to-date findings on the various inflammatory markers identified so far and its clinical usefulness.

Keywords: C-Reactive Protein, Interlukins, Diabetes Mellitus, Tumor Necrosis Factor.

1. INTRODUCTION

It has been well known that high sensitive C-reactive protein(hs-CRP) is an independent marker of the risk of Cardio Vascular Disease (CVD), but the predictive capacity remains controversial, but many prospective studies have observed that hs-CRP shows increased risk of Type 2 Diabetes Mellitus (T2DM). High consumption of vegetables and fruits are associated with lower levels of circulating hs-CRP, perhaps by exerting anti-inflammatory effects. Both mechanistic and epidemiologic studies regarding dietary factors and low-grade inflammation are necessary to add to our knowledge of dietary influence on chronic disease development [1]. Routine hs-CRP measurement will be useful to assess cardio metabolic syndrome to improve detection of risk for both diabetes and cardiovascular events in patients. Multiple clinical studies are now underway that are evaluating whether agents traditionally used to improve glycemic control may also significantly reduce hs-CRP[2]. Type 1 Diabetes Mellitus(T1DM) is a pro inflammatory state, as evidenced by increased levels of monocyte Interlukin-6(IL-6), superoxide anion, and plasma CRP, soluble inflammation cell adhesion molecule(sICAM), sCD40L, and Nitro Tyrosine(NT). All these have a major implication on our understanding of the role of inflammation in vasculopathies in T1DM[3]. Serum hs-CRP showed significant correlation to 24hrs urine albumin excretion and Metabolic Syndrome (MS) and might be used as the future criteria of MS. Among microvascular complications, only diabetic nephropathy was found to be associated with hs-CRP level, suggesting that inflammatory process plays a role in nephropathy in T2DM[4].

Alterations in innate immune pathways are detectable in genetically susceptible individuals and could be linked with the early course of T1DM[5]. IL-6 causes vascular smooth muscle contraction in abdominal aorta of rats with T1DM [6]. Strong interaction effects between age and diabetes and Body Mass Index(BMI) were observed for IL-8, resistin and hs-CRP. The cytokine/adipokine profiles of Mexican Americans with diabetes suggest an association between low-grade inflammation and quality of glucose control. Unique to in our population is that the chronic inflammation is accompanied by lower levels of leptin[7]. It is imperative that researchers recognize and acknowledge the limitations of the leptin/leptin receptor- based rodent models and invest in research methods that would be

directly and reliably applicable to humans in order to advance T2DM management[8]. Data do not support an insulin sensitizing effect of n-3 Polyunsaturated Fatty Acids by means of influencing circulating adipocytokines[9]. Both chronic and acute exercise influence the phosphorylation and expression of components of the Adenosine Mono phosphate activated Protein Kinase (AMPK) and downstream to PIK3 (aPKC, Akt), and improve Glucose Transporter type4(GLUT4) trafficking in skeletal muscle[10].

Diversity in adiposity, age and sex could not account for the heterogeneity across different studies. In a study there was no substantial associations between the common polymorphisms in IL6 gene and circulating IL-6 levels and the risk of T2DM[11]. Elevated IL-6 concentration is associated with diabetes-related variables which could accelerate progression of microvascular complications in T1DM patients[12]. IL-6 gene -174 G/C polymorphism is not associated with T1DM risk. However, due to small sample sizes included in most of the studies and the selection bias existed in some studies, the results should be interpreted with caution[13]. Expression of Toll Like Receptor-4 (TLR4) in db/db mouse islets increased in parallel with hyperglycaemia. A similar increase in expression and secretion of TNF-α, IL-1 and IL-6 was observed. In addition to its contribution to insulin resistance, TLR4 might also play a role in β-cell dysfunction in T2DM[14].

Glyburide treatment of diabetes decreased hs-CRP and did so even though body weight increased. Both hs-CRP and adiponectin correlate strongly to insulin sensitivity. hs-CRP in contrast to adiponectin, is far more dependent on adiposity. The relationship between hs-CRP like leptin and gender depends on how CRP is expressed relative to adiposity. These observations raise the possibility that gender differences in adiponectin may be lost in diabetes. Pharmacologic treatment of diabetes may modulate CRP independent of adiposity[15]. hsCRP values of both gestational diabetic (GD) and non-diabetic pregnant women were significantly higher compared to controls. Significant negative correlations were found between serum selenium and total cholesterol, low-density lipoprotein cholesterol(LDL), and hs-CRP values indicating that low selenium levels are associated with increased lipid peroxidation. Serum selenium concentrations of Hungarian pregnant women are low compared to internationally published data[16]. Multivariate regression analysis using mean common cardiac artery - Intima-media thickness (CCA-IMT) as the dependent variable identified only age, hs-CRP and diastolic blood pressure as independent determinants of mean CCA-IMT. While hs-CRP associates with insulin resistance and subclinical atherosclerosis in early-state T2DM, hs-CRP is a useful marker of subclinical atherosclerosis in early-state T2DM independent of factors that directly reflect insulin resistance[17]. T2DM patients with metabolic syndrome MS have elevated markers of inflammation and evidence of cardiac sympathetic predominance. High serum concentrations of hs-CRP are associated with relative cardiac sympathetic over activity during the early morning in T2DM patients[18].

Increased placental leptin (PL) and placental leptin receptor gene (LEPR) expression may have a role in stimulating fetal overgrowth in T1DM pregnancy[19]. Parameters such as age, Waist to Hip ratio(WHR), Fasting plasma glucose (FPG), HbA1C, LDL, HDL, Total Cholesterol and Family History were significantly different among the subjects with Gln223Agr polymorphism of LEPR[20]. Vitamin D3 supplementation significantly increased serum leptin and osteoprotegerin (OPG) levels. Further, large-scale clinical trials are warranted to confirm these results[21]. Obesity mainly central type might be responsible for insulin resistance in T2DM whereas leptin, a potential marker for obesity, may not. This perhaps points towards the multifactorial causation of insulin resistance in T2DM[22]. In a large cohort study of Sudanese subjects with T2DM sherved circulating leptin levels are lower in diabetic subjects than in controls of similar age and BMI. The lower serum leptin in diabetic subjects may be a consequence of differences in fat distribution[23]. Leptin levels correlated significantly with CRP in healthy controls and in patients with newly diagnosed diabetes before, and after metformin therapy, while there was no significant correlation between leptin and CRP in patients with long-standing diabetes. After multiple adjustments for potential confounders, leptin was the best predictor of CRP in controls, and in patients with newly diagnosed T2DM who received metformin. Statin treatment did not have any significant effect on the results[24].

Palmitate or oleate pre treatment combined with a leptin antagonist induced Receptor for Advanced Glycation End products (RAGE) expression, advanced glycation end products (AGE)-elicited apoptosis, and impaired glucose-stimulated insulin secretion by AGE in MIN6 cells. Free Fatty Acid(FFA) elevation with concomitant AGE formation during prolonged hyperglycemia could cause β-cell damage through insufficient leptin action and subsequent RAGE induction in T2DM[25]. The increased expression of leptin and LEPR may contribute to these effects.

These results may provide a possible mechanism for the previously observed increase in placenta growth in GDM[26]. Leptin therapy is an effective and safe treatment for therapy-resistant diabetes and hypertriglyceridemia in patients with congenital lipodystrophy[27]. Leptin may be an effective therapeutic option for both T1DM and T2DM. However, short-term human clinical studies in overweight and obese patients with recently diagnosed T2DM have reported minimal efficacy of leptin administration to lower blood glucose levels[28].

TNF-α acutely lowers basal plasma insulin levels but does not impair glucose-stimulated insulin secretion. The mechanisms behind this are unknown but it may be due to TNF-α increasing clearance of insulin from plasma without impairing beta-cell function or hepatic insulin sensitivity[29]. Though TNF-α G-238A and G-308A polymorphisms were not involved in the pathogenesis of T2DM, but such patients carrying TNFA-α or TNF-308*2 genotype might be more susceptible to diabetic complications such as atherosclerosis[30]. A state of subclinical inflammation defined and quantifiable by inflammatory score including TNF-α, IL-6, Monocyte Chemo attractant Protein-1(MCP-1), osteopontin, fractalkine and adiponectin is associated with both hyperglycemia and whole body insulin resistance in T2DM[31]. The TNF-α concentrations in tears increase with the severity of pathology and were lower in control group than in diabetic subjects. The level of TNF-α is highly correlated with severity of diabetic retinopathy and with nephropathy. Tear fluid collection may be a useful non invasive method for the detection of proliferative diabetic retinopathy[32]. Inflammation is important in the pathogenesis of Diabetic Nephropathy (DN) and indicate that TNF-α may be used as an independent predictor for the progression of DN at the early stage[33].

TNF-α -308A variant could be a risk factor for the development of T2DM, particularly in Asian subjects. However, this association was not statistically significant in Caucasian subjects. More specified ethnical studies are required to reveal the detailed physiological characteristics of the TNF-α -308 G/A polymorphism[34]. TNF-α is a significant risk factor for more severe periodontal disease because, as compared to non-diabetics, diabetic subjects react with an abnormally high degree of inflammation to an equivalent bacterial burden[35]. TNF-α secretion phenotype (4.6-fold increase) which, in the presence of Gram-negative bacterial challenge, is associated with a more severe periodontal disease expression. In addition, approximately 40% T1DM periodontitis patients demonstrated a 62-fold elevation in TNF-α secretion relative to non-diabetic gingivitis or periodontitis patients and a 13.5-fold increase relative to T1DM group A (gingivitis or mild periodontitis) patients[36]. The expression of IL-6 has an effect on obesity and the metabolism of glucose and lipid in diabetic mice and that the expression site of IL-6 is not an important factor[37].

Diabetic heterozygous superoxide dismutase 2 (SOD2) mice had no evidence of increased renal disease, and Ampka2 (-/-) mice had increased albuminuria that was not reduced with Amino Imidazole Carboxamido Ribonucleotide (AICAR) treatment. Reduction of mitochondrial superoxide production with rotenone was sufficient to reduce AMPK phosphorylation in mouse kidneys. Taken together, these results demonstrate that diabetic kidneys have reduced superoxide and mitochondrial biogenesis and activation of AMPK enhances superoxide production and mitochondrial function while reducing disease activity[38]. AMPK activator 5-aminoimidazole-4-carboxamide 1-β-d-ribofuranoside and the antihyperglycemic drug metformin mimicked protective effects of C-peptide. C-peptide replacement therapy normalized hyperglycemia-induced AMPKα dephosphorylation, Reactive Oxygen Species (ROS) generation and mitochondrial disorganization in aorta of diabetic mice, highlighting a novel mechanism by which C-peptide activates AMPKα and protects against hyperglycemia-induced vasculopathy[39]. There is evidence that both metformin and aspirin provide some protection against development of cancer in humans, and whether AMPK might be involved in these effects is also not clear[40]. AMPK activation by Low Molecular Weight Fucoidan (LMWF) could prevent metabolic diseases by controlling the ER stress-dependent pathway and that this beneficial effect of LMWF provides a potential therapeutic strategy for ameliorating Endoplasmic Reticulum (ER) stress-mediated metabolic dysfunctions[41]. Combining GC/MS profiling with random forest is a useful approach to analyze metabolites and to screen the potential biomarkers for exploring the relationships between AMPK and DM[42]. The combination of IA-2A and/or Glutamate Decarboxylase A (GADA) had a higher sensitivity for T1DM than Internal Carotid Arteries(ICA) alone. The close association between IA-2A and HLA DR4, the strongest single allele predisposing to T1DM, suggests that IA-2A may be a more specific marker of beta-cell destruction than GADA, which have been shown toassociate with the DR3 allele and thyroid autoimmunity[43].

Patients with newly diagnosed T1DM manifest significantly lower apoTf serum levels compared to healthy controls and patients with long-lasting disease, suggesting that apoTf pivotal role in the perpetuation of T1DM pathology[44]. Quantitative determination of interleukin-8 (IL-8), ferritin and soluble transferring receptor (sTFR) could help in predicting T2DM-associated immuno-inflammatory manifestations characterize the micro-and macrovascular disease complications, particularly for high risk populations[45]. A rise in serum Sialic Acid (SA) and a decrease in Carbohydrate-Deficient Transferrin (CDT) concentrations were observed in both diabetic groups with and without complications, and there were no differences between the two groups of patients. There was a statistically significant correlation between serum SA and CDT in diabetic subjects with microvascular complications, but not in patients without such complications. This proves that the serum changes in CDT and SA levels in the course of T2DM are associated with each other in the presence of microangiopathy[46]. Oxygen free radicals are formed in DM and can result in diabetic complications and that a prooxidant/oxidant imbalance is involved in tissue injury in DM and diabetic complications[47].

Plasma total thiol (T-SH) was not different between diabetic patients and the controls. Serum nitrotyrosine (NT), nitric oxide (NO), and erythrocyte superoxide dismutase (SOD) levels were not different either between three groups of diabetic patients or between the patients and their controls. Changes in markers of oxidative stress other than NT, NO, and SOD observed in adolescent and young adult early stage T1DM patients contribute to the imbalance in the redox status of the plasma. This imbalance may be due to metal-catalyzed protein oxidation in both groups of T1DM patients clinically free from complications[48]. Although redox status of plasma is impaired in diabetic patients, but these significantly different markers reflect enhanced oxidative protein damage in diabetic patients with complications[49]. The exact mechanisms by which growth hormone (GH) damages the kidney inducing diabetic nephropathy has not yet been elucidated. Recently, it has been shown that transferrin has the same diabetogenic effects as that of GH, being its mediator. Selective deposition of transferrin was associated with signs of organelle and cytoskeleton damage. On the basis of previous evidence and present glomerular findings, these results suggest an indirect diabetogenic effect on the kidney by GH mediated through transferring[50]. CRP is increased in some patients by severe diabetic ketoacidosis (DKA) and its treatment, and that DKA can be associated with a non-infectious form of systemic inflammatory response syndrome (SIRS)[51].

While univariate analysis has established that age, Diabetes Mellitus (DM), presence of CVD, low prealbumin all are associated with patient survival, multivariate analysis demonstrates that DM, older age, CVD, hs-CRP were independent predictors for mortality in incident Peritoneal Dialysis(PD) patients[52]. Preoperative prealbumin levels could be a useful marker for predicting complications, especially infectious complications, after gastric surgery[53]. Circulating Retinol-binding Protein 4 (RBP4) and Transthyretin (TTR) were not affected by human obesity or T2DM, which might be attributed to the absence of alterations of TTR isoforms and the ratio of holo- and apo-RBP4 that might modify the TTR-RBP4 interaction[54]. Alpha1-Antitrypsin (AAT) gene therapy attenuates cell-mediated autoimmunity, alters the T cell receptor repertoire, and efficiently prevents T1DM in the Non Obese Diabetic (NOD) mouse model. These results strongly suggest that rAAV1-mediated AAT gene therapy may be useful as a novel approach to prevent T1DM [55].

Haptoglobin (HP) genotype is significantly associated with the development of reduced Glomerular Filtration Rate (GFR) and End-Stage Renal Disease (ESRD) in the Diabetes Control as observed in Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study[56]. Vitamin E administration to HP 2-2 DM mice resulted in a significant decrease in both intralysosomal iron-induced oxidation and lysosomal destabilization. Iron-induced renal tubular injury may play a major role in the development of diabetic nephropathy and may be a target for slowing the progression of renal disease[57]. Temporary changes in HP expression strongly correlated with the serum levels of TNF-α and IL-6. Lower HP expression at the fourth week and thereafter correlated with a decrease in TNF-α concentration and changes in the TNF-α/IL-6 ratio. If glutathione/glutathione disulfide (GSH/GSSG) ratio and antioxidant enzyme activities in liver decreased at the end of fourth week,there it could be concluded that the liver was exposed to oxidative stress and injury which in the presence of the above-mentioned inflammatory mediators lead to different HP expression profiles at different stages of DM. An inverse correlation was observed between the HP and free iron serum levels in diabetic rats. The higher levels of HP during the first 2 weeks were accompanied by a lower level of free iron. In view of the established function of HP, a possible role in decreasing oxidative stress during the early stage of diabetes

has been postulated[58]. HP is an acute phase protein with antioxidant and immunomodulatory properties. Three main genotypes/phenotypes (Hp1-1, Hp2-1 and Hp2-2) show distinct efficiencies in these activities and have been associated with susceptibility and outcome in several diseases, including DM. Polymorphism of HP is not associated with the presence of Diabetic Retinopathy (DR) in the Brazilian population studied[59].

Recent studies show that nearly 13% of Asian Indian children and young adults in India have subclinical inflammation, and approximately 20% have insulin resistance, portending high risk for coronary heart disease (CHD) in adulthood. Possible determinants of high hs-CRP levels in Asian Indians might be excess body fat, including high subcutaneous fat, and physical inactivity. The relationships of recurrent infections, protein deficiency, and subclinical inflammation in Asian Indians remain uninvestigated. Prevention of childhood adiposity is critical to decrease future risk for development of T2DM and CHD, particularly in highly predisposed ethnic groups such as Asian Indians and South Asians[60]. Women with diabetes but without previous myocardial infarction (MI) were more similar to women with previous MI (both with and without diabetes) than to the healthy controls. Compared with healthy women, the women with diabetes and/or MI had higher IgG and lower IgM antibody titres against oxidized low density lipoprotein (LDL) and higher CRP levels that were independent of other cardiovascular risk factors. These findings might indicate a differentiated immune response against modified LDL, more pronounced inflammation and a more aggressive atherosclerotic process in women with diabetes[61]. Some of the risk factors associated with CHD in T1DM patients are also independently predictive of high CRP concentrations. The reasons for this, and whether intervention would prove useful, require further investigation[62]. Circulating levels of $sTNF\alpha R_1$ are independently associated with the cumulative incidence of ESRD. This association is both significant and biologically plausible and appears to provide added value as a biomarker, based on the absolute values of net reclassification index (NRI) and integrated discrimination improvement (IDI)[63]. Hyperglycemia primes palmitate stimulated blood cells for NO, IL-6, and TNF-alpha secretion under in vitro free fatty acids (FFA) stimulation are associated with the secretion of inflammatory biomarkers in diabetes. A combined therapy targeting signaling pathways activated by hyperglycemia in conjunction with simultaneous control of hyperglycemia and hypertriglyceridemia would be suggested for controlling the progress of diabetic complications [64].

The finding of novel pharmacologic agents proficient to improve plasma adiponectin (APN) levels should be target of exhaustive research. Interesting future approaches could be the development of APN -targeted drugs chemically designed to induce the activation of its receptors and/or post receptor signaling pathways, or the development of specific APN agonists[65]. APN signaling pathways comprise at least two putative receptors (AdipoR1 and AdipoR2). Ways to enhance adiponectin bioactivity are actively being sought. In obesity, reducing chronic adipose-tissue inflammation and macrophage infiltration into it could be beneficial to reverse down regulation of APN gene expression by pro-inflammatory cytokines. Pharmacologically, thiazolidinediones and cannabinoid-1 receptor blockers (e.g.,rimonabant) increase plasma APN and gene expression in adipocytes. Finally, AdipoR activation to mimic APN actions could prove beneficial to reduce metabolic risk factors in conditions, such as obesity, where low adiponectinemiaprevails[66]. Even though pregnant women are diagnosed as GDM according to the new International Diabetes in Pregnancy Consensus Group (IADPSG) criteria, the APN SNP45 may be closely correlated with the prevalence of GDM in Han women of Nantong area in China, and the allele +45G in APN gene might be associated with reduced plasma APN levels and adverse pregnancy outcomes[67].

Myocardial AdipoR1 protein expression was positively correlated with myocardial APN levels, and negatively correlated with Fasting insulin (FINS) and HOMA-IR. Myocardial and serum levels of APN are reduced in rats with Diabetic Cardiomyopathy (DC). Metabolic disorders of blood glucose and lipid levels, as well as IR, are associated with low APN levels. Furthermore, low levels of myocardial Adipo1R mRNA and protein expression correlate with reduced insulin sensitivity[68]. APN gene polymorphisms might be effective on susceptibility for T2DM development which emerged from the interactions between multiple genes, variants and environmental factors[69]. ALDH2 protects against diabetes-induced myocardial dysfunction possibly through an adenosine monophosphate-activated protein kinase (AMPK) -dependent regulation of autophagy[70]. AMPK activators alleviate tissue inflammation and promote re-epithelialization in diabetic wounds. However, due to the complicated pathological mechanism of diabetic foot ulcers, AMPK activators should be combined with other approaches. The new strategies for

combination therapy with AMPK activator may provide a therapeutic advantage for patients with diabetic ulcers[71].

Autoantibodies against oxidised LDL (ox LDL) indicate the presence of oxidatively modified LDL in vivo, but their titers in the serum do not seem to associate with the excess cardiovascular mortality, morbidity, or intimal-medial thickness of the carotid artery[72]. Abnormal serum IgA concentrations are very common in diabetic patients and that further research should be carried out to verify whether the determination of serum immunoglobulins, IgA in particular, is of clinical use for monitoring diabetes or evaluating its secondary effects[73]. Progression to clinical onset of T1DM is associated with a maturation and a decrease in the Th2 immune response against GAD65; findings which could have implications for future intervention and prediction strategies[74]. The strengths of association between periodontitis and diabetes were stronger in people having elevated serum CRP and P gingivalistiters. This may suggest that chronic inflammatory condition could increase the impact of periodontitis on hyperglycaemicstatus[75]. Metabolic regulation of B-1 cells is of importance for the understanding of the role of this cell type in life-style-related condition[76]. The continued increase in IgG levels by age indicates that adult levels are reached later than in previously studied cohorts, thereby indicating a slower maturation of the immune system[77].

Differences in IgM antibody concentrations by nephropathy classification were not supported by the data. The predominance of pro-inflammatory IgGoxLDL antibodies is associated with existence of diabetic nephropathy, and a protective role of IgM antibodies could not be demonstrated[78]. Magnesium deficit has profound immunosuppressive capabilities in patients with T1DM by significantly reducing the number of IgG synthesizing cells and serum IgGconcentrations[79]. Deposition of immunoglobulins is a component of diabetic microangiopathy. Differences in expression of HLA-DR in glomeruli between diabetics and non-diabetics remain to be explored[80].

2. CONCLUSION

Among the various inflammatory markers discussed in this review article, hs-CRP marker is found to be useful in many diseases such as CVD, T2DM andin various infectious diseases and is a promising diagnostic tool for metabolic syndrome. The other inflammatory markers found to be useful are IL-6, leptin, TNF-α, adiponectin, apoTf, SA, SOD, CDT, prealbumin, hepatoglobin and transferrin. The inflammatory markers highlighted in this review article will make awareness among research scholars to undertake specific disease based analysis of inflammatory markers for diagnostic purpose and to develop cost effective methodologies for clinical purposes.

3. REFERENCES

1. Nanri A, Moore MA and Kono S. Impact of C-reactive protein on disease risk and its relation to dietary factors. **Asian Pac J Cancer Prev.** 2007; 8(2):167-77.
2. Ndumele CE, Pradhan AD and Ridker PM. Interrelationships between inflammation, C-reactive protein, and insulin resistance**. J Cardiometa b Syndr.** 2006; 1(3):190-6.
3. Devaraj S, Glaser N, Griffen S, Wang-Polagruto J, Miguelino E and JialalI. Increased monocytic activity and biomarkers of inflammation in patients with type 1 diabetes. **Diabetes.** 2006; 55(3):774-9.
4. Kang ES, Kim HJ, Ahn CW, Park CW, Cha BS, Lim SK, Kim KR, Lee HC. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. **Diabetes Res Clin Pract.** 2005; 69(2):151-9.
5. Alkanani AK, Rewers M, Dong F, Waugh K, Gottlieb PA and Zipris D. Dysregulated Toll-like receptor-induced interleukin-1β and interleukin-6 responses in subjects at risk for the development of type 1 diabetes. **Diabetes.** 2012; 61(10): 2525-33.
6. Tang WB, Zhou YQ, Zhao T, Shan JL, Sun P, Yang TT, Chang XW, Li S, Wang PS and Xie DP. Effect of interleukin-6 (IL-6) on the vascular smooth muscle contraction in abdominal aorta of rats with streptozotocin-induced diabetes. **Chin J Physiol.** 2011; 31; 54(5): 318-23.
7. Mirza S, Hossain M, Mathews C, Martinez P, Pino P, Gay JL, Rentfro A, McCormick JB and Fisher-Hoch SP. Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: a cross-sectional study. **Cytokine.** 2012; 57(1): 136-42.
8. Wang B, Chandrasekera PC and Pippin JJ. Leptin- and leptin receptor-deficient rodent models: relevance for human type 2 diabetes. **Curr Diabetes Rev.** 2014; 10(2): 131-45.
9. Stirban A, Nandrean S, Gotting C, Stratmann B and Tschoepe D. Effects of n-3 Polyunsaturated Fatty Acids (PUFAs) on Circulating Adiponectin and Leptin in Subjects

with Type 2 Diabetes Mellitus. **Horm Metab Res.** 2014; 46(7): 490-2.

10. Cao S, Li B, Yi X, Chang B, Zhu B, Lian Z, Zhang Z, Zhao G, Liu H and Zhang H. Effects of exercise on AMPK signaling and downstream components to PI3K in rat with type 2 diabetes. **PLoS One.** 2012; 7(12):e51709.
11. Qi L, van Dam RM, Meigs JB, Manson JE, Hunter D and Hu FB.Genetic variation in IL6 gene and type 2 diabetes: tagging-SNP haplotype analysis in large-scale case-control study and meta-analysis. **HumMol Genet.** 2006; 15(11):1914-20.
12. Wegner M, Araszkiewicz A, Piorunska-Stolzmann M, Wierusz-Wysocka B, Zozulinska-Ziolkiewicz D. Association between IL-6 concentration and diabetes-related variables in DM1 patients with and without micro vascular complications. **Inflammation.** 2013; 36(3):723-8.
13. Yin YW, Sun QQ, Zhang BB, Hu AM, Wang Q, Liu HL, Hou ZZ, Zeng YH, Xu RJ and Shi LB. The lack of association between interleukin-6 gene -174 G/C polymorphism and the risk of type 1 diabetes mellitus: a meta-analysis of 18,152 subjects. **Gene.** 2013; 25; 515(2):461-5.
14. Ladefoged M, Buschard K, Hansen AM. Increased expression of toll-like receptor 4 and inflammatory cytokines, interleukin-6 in particular, in islets from a mouse model of obesity and type 2 diabetes. **APMIS.** 2013; 121(6):531-8.
15. Putz DM, Goldner WS, Bar RS, Haynes WG and Sivitz WI. Adiponectin and C-reactive protein in obesity, type 2 diabetes, and monodrug therapy. **Metabolism.** 2004; 53(11): 1454-61.
16. Molnar J, Garamvolgyi Z, Herold M, Adanyi N, Somogyi A and Rigo J Jr.Serum selenium concentrations correlate significantly with inflammatory biomarker high-sensitive CRP levels in Hungarian gestational diabetic and healthy pregnant women at mid-pregnancy. **Biol Trace Elem Res.** 2008; 121(1): 16-22.
17. Mita T, Watada H, Uchino H, Shimizu T, Hirose T, Tanaka Y and Kawamori R. Association of C-reactive protein with early-stage carotid atherosclerosis in Japanese patients with early-state type 2 diabetes mellitus. **Endocr J.** 2006; 53(5): 693-8.
18. Aso Y, Wakabayashi S, Nakano T, Yamamoto R, Takebayashi K and Inukai. High serum high-sensitivity C-reactive protein concentrations are associated with relative cardiac sympathetic over activity during the early morning period in type 2 diabetic patients with metabolic syndrome. **Metabolism.** 2006; 55(8): 1014-21.
19. Iciek R, Wender-Ozegowska E, Zawiejska A, Mikolajczak P, Mrozikiewicz PM, Pietryga M and Brazert J.Placental leptin and its receptor genes expression in pregnancies complicated by type 1 diabetes. **J Physiol Pharmacol.** 2013; 64(5): 579-85.
20. Etemad A, Ramachandran V, Pishva SR, Heidari F, Aziz AF, Yusof AK, Pei CP, Ismail P. Analysis of Gln223Agr polymorphism of Leptin Receptor Gene in type II diabetic mellitus subjects among Malaysians. **Int J Mol Sci.** 2013; 14(9): 19230-44.
21. Maggi S, Siviero P, Brocco E, Albertin M, Romanato G and Crepaldi G.Vitamin D deficiency, serum leptin and osteoprotegerin levels in older diabetic patients: an input to new research avenues. **Acta Diabetol.** 2014; 51(3): 461-9.
22. Das P, Bhattacharjee D, Bandyopadhyay SK, Bhattacharya G and Singh R. Association of obesity and leptin with insulin resistance in type 2 diabetes mellitus in Indian population. **Indian J Physiol Pharmacol.** 2013; 57(1): 45-50.
23. Abdelgadir M, Elbagir M, Eltom M, Berne C and Ahren B. Reduced leptin concentrations in subjects with type 2 diabetes mellitus in Sudan. **Metabolism.** 2002; 51(3):304-6.
24. Morteza A, Nakhjavani M, Asgarani F, Ghaneei A, Esteghamati A and Mirmiranpour H. The lost correlation between leptin and CRP in type 2 diabetes. **Eur Cytokine Netw.** 2013; 24(1): 53-9.
25. Han D, Yamamoto Y, Munesue S, Motoyoshi S, Saito H, Win MT, Watanabe T, Tsuneyama K and Yamamoto H. Induction of receptor for advanced glycation end products by insufficient leptin action triggers pancreatic β-cell failure in type 2 diabetes. **Genes Cells.** 2013; 18(4):302-14.
26. Perez-Perez A, Maymo JL, Gambino YP, Guadix P, Duenas JL, Varone CL and Sanchez-Margalet V. Activated translation signaling in placenta from pregnant women with gestational diabetes mellitus: possible role of leptin. **Horm Metab Res.** 2013; 45(6): 436-42.
27. Jazet IM, Jonker JT, Wijngaarden MA, Lamb H, Smelt AH. Therapy resistant diabetes mellitus and lipodystrophy:

leptin therapy leads to improvement. **NedTijdschrGeneeskd.** 2013; 157(4): A5482.

28. Cummings BP. Leptin therapy in type 2 diabetes. **Diabetes Obes Metab.** 2013; 15(7): 607-12.
29. Ibfelt T, Fischer CP, Plomgaard P, van Hall G and Pedersen BK.The acute effects of low-dose TNF-α on glucose metabolism and β-cell function in humans. **Mediators Inflamm.** 2014: 29-5478.
30. Shiau MY, Wu CY, Huang CN, Hu SW, Lin SJ and Chang YH.TNF-alpha polymorphisms and type 2 diabetes mellitus in Taiwanese patients. **Tissue Antigens.** 2003; 61(5): 393-7.
31. Daniele G, Guardado Mendoza R, Winnier D, Fiorentino TV, Pengou Z, Cornell J, Andreozzi F, Jenkinson C, Cersosimo E, Federici M, Tripathy D and Folli F. The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. **ActaDiabetol.** 2014; 51(1): 123-31.
32. Costagliola C, Romano V, De Tollis M, Aceto F, dell'Omo R, Romano MR, Pedicino C and Semeraro F. TNF-alpha levels in tears: a novel biomarker to assess the degree of diabetic retinopathy. **Mediators Inflamm.** 2013: 629-529.
33. Wu J, Ding Y, Zhu C, Shao X, Xie X, Lu K, Wang R. Urinary TNF-α and NGAL are correlated with the progression of nephropathy in patients with type 2 diabetes. **Exp Ther Med.** 2013; 6(6):1482-1488.
34. Zhao Y, Li Z, Zhang L, Zhang Y, Yang Y, Tang Y, Fu P. The TNF-alpha -308G/A polymorphism is associated with type 2 diabetes mellitus: an updated meta-analysis. **Mol Biol Rep.** 2014; 41(1): 73-83.
35. Salvi GE, Beck JD and Offenbacher S. PGE2, IL-1 beta, and TNF-alpha responses in diabetics as modifiers of periodontal disease expression. **Ann Periodontol.** 1998; 3(1): 40-50.
36. Salvi GE, Collins JG, Yalda B, Arnold RR, Lang NP and Offenbacher S. Monocytic TNF alpha secretion patterns in IDDM patients with periodontal diseases. **J Clin Periodontol.** 1997; 24(1): 8-16.
37. Mukumoto H, Takahashi Y, Ando M, Nishikawa M and Takakura Y. Expression profile-dependent improvement of insulin sensitivity by gene delivery of interleukin-6 in a mouse model of type II diabetes. **Mol Pharm.** 2013; 10(10): 3812-21.
38. Dugan LL, You YH, Ali SS, Diamond-Stanic M, Miyamoto S, DeCleves AE, Andreyev A, Quach T, Ly S, Shekhtman G, Nguyen W, Chepetan A, Le TP, Wang L, Xu M, Paik KP, Fogo A, Viollet B, Murphy A, Brosius F, Naviaux RK and Sharma K. AMPK dysregulation promotes diabetes-related reduction of superoxide and mitochondrial function. **J Clin Invest.** 2013; 123(11): 4888-99.
39. Bhatt MP, Lim YC, Kim YM and Ha KS. C-peptide activates AMPKα and prevents ROS-mediated mitochondrial fission and endothelial apoptosis indiabetes. **Diabetes.** 2013; 62(11): 3851-62.
40. Hardie DG. AMPK: a target for drugs and natural products with effects on both diabetes and cancer. **Diabetes.** 2013; 62(7): 2164-72.
41. Jeong YT, Kim YD, Jung YM, Park DC, Lee DS, Ku SK, Li X, Lu Y, Chao GH, Kim KJ, Lee JY, Baek MC,Kang W, Hwang SL, Chang HW. Low molecular weight fucoidan improves endoplasmic reticulum stress-reduced insulin sensitivity through AMP-activated protein kinase activation in L6 myotubes and restores lipid homeostasis in a mouse model of type 2diabetes. **Mol Pharmacol.** 2013; 84(1):147-57.
42. Huang JH, He RH, Yi LZ, Xie HL, Cao DS, Liang YZ. Exploring the relationship between 5'AMP-activated protein kinase and markers related to type 2 diabetes mellitus. **Talanta.** 2013; 15; 110: 1-7.
43. Savola K, Bonifacio E, Sabbah E, Kulmala P, Vahasalo P, Karjalainen J, Tuomilehto-Wolf E, Meriläinen J, Akerblom HK and Knip M. IA-2 antibodies - a sensitive marker of IDDM with clinical onset in childhood and adolescence. Childhood Diabetesin Finland Study Group. **Diabetologia.** 1998; 41(4): 424-9.
44. Mangano K, Fagone P, Di Mauro M, Ascione E, Maiello V, Milicic T, Jotic A, Lalic NM, Saksida T, Stojanovic I, Selmi C, Farina C, Stosic-Grujicic S, Meroni P and Nicoletti F. Theimmunobiology of apotransferrin in type 1 diabetes. **Clin ExpImmunol.** 2012; 169(3): 244-52.
45. Abou-Shousha S, Abd El-Megeed MH, Sultan HK. Interleukin-8, ferritin and soluble transferring receptors in type II diabetes mellitus. **Egypt J Immunol.** 2006; 13(1): 19-25.

46. Cylwik B, Chrostek L, Jakimiuk B, Popławska A and Szmitkowski M. Serum level of sialic acid (SA) and carbohydrate-deficient transferring (CDT) in type 2 diabetes mellitus with micro vascular complications. **J Clin Lab Anal.** 2006; 20(2): 68-73.
47. Memişoğullari R and Bakan E. Levels of ceruloplasmin, transferring and lipid peroxidation in the serum of patients with Type 2 diabetes mellitus. **J Diabetes Complications.** 2004; 18(4):193-7.
48. Telci A, Cakatay U, Salman S, Satman I and Sivas A. Oxidative protein damage in early stage Type 1 diabetic patients. **Diabetes Res Clin Pract.** 2000; 50(3): 213-23.
49. Cakatay U, Telci A, Salman S, Satman L and Sivas A. Oxidative protein damage in type I diabetic patients with and without complications. **Endocr Res.** 2000; 26(3): 365-79.
50. Gonzalez S, Vargas L. Diabetogenic transferring damages podocytes in early human diabetic nephropathy. **HormMetab Res.** 2001; 33(2): 84-8.
51. Dalton RR, Hoffman WH, Passmore GG, Martin SL. Plasma C-reactive protein levels in severe diabetic ketoacidosis. **AnnClin Lab Sci.** 2003; 33(4): 435-42.
52. Owen Kwon, Jang-Hee Cho, Chung-Hoon Yu, Ga-Young Park, Jun-Seop Kim, Yoon-Jung Kang, Ji-Young Choi, Tae-Du Jung, Chan-Duck Kim, Yong-Lim Kim, Sun-Hee Park. The Association of Prealbuminwith Nutritional Markers and Inflammation in Incident Peritoneal Dialysis Patients. **Kidney Research and Clinical Practice.** 2012; 31(2): 47.
53. Bae, Hye-Jung, Lee, Hyuk-Joon, Han, Dong-Seok, Suh, Yun-Suhk, Lee, Yong-Hwa, Lee, Hye-Suk, Cho, Jae-Jin, Kong, Seong-Ho and Yang, Han-Kwang. Prealbumin Levels as a Useful Marker for Predicting Infectious Complications after Gastric Surgery. **Journal of Gastrointestinal Surgery.** 2011.
54. Frey SK, Spranger J, Henze A, Pfeiffer AF, Schweigert FJ and Raila J. Factors that influence retinol-binding protein 4-transthyretin interaction are not altered in overweight subjects and overweight subjects with type 2 diabetes mellitus. **Metabolism.** 2009; 58(10):1386-92.
55. Lu Y, Tang M, Wasserfall C, Kou Z, Campbell-Thompson M, Gardemann T, Crawford J, Atkinson M and Song S. Alpha1-antitrypsin gene therapy modulates cellular immunity and efficiently prevents type 1 diabetes in nonobese diabetic mice. **Hum Gene Ther.** 2006; 17(6): 625-34.
56. Orchard TJ, Sun W, Cleary PA, Genuth SM, Lachin JM, McGee P, Paterson AD, Raskin P, Anbinder Y and Levy AP. Haptoglobin genotype and the rate of renal function decline in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. **Diabetes.** 2013; 62(9): 3218-23.
57. Asleh R, Nakhoul FM, Miller-Lotan R, Awad H, Farbstein D, Levy NS, Nakhoul N, Iancu TC, Manov I, Laue M, Traber MG, Lebold KM and Levy AP. Poorlysosomal membrane integrity in proximal tubule cells of haptoglobin 2-2 genotype mice with diabetes mellitus. **Free Radic Biol Med.** 2012; 15; 53(4): 779-86.
58. Jelena A, Mirjana M, Desanka B, Svetlana IM, Aleksandra U, Goran P and Ilijana G. Haptoglobin and the inflammatory and oxidative status in experimental diabetic rats: antioxidant role of haptoglobin. **J Physiol Biochem.** 2013; 69(1): 45-58.
59. Wobeto VP, Rosim ET, Melo MB, Calliari LE and Sonati Mde F.Haptoglobin polymorphism and diabetic retinopathy in Brazilian patients. **Diabetes Res Clin Pract.** 2007; 77(3): 385-8.
60. Misra A. C-reactive protein in young individuals: problems and implications for Asian Indians. **Nutrition.** 2004; 20(5): 478-81.
61. Dotevall A, Hulthe J, Rosengren A, Wiklund O and Wilhelmsen L. Autoantibodies against oxidized low-density lipoprotein and C-reactive protein are associated with diabetes and myocardial infarction in women. **ClinSci (Lond).** 2001; 101(5): 523-31.
62. Kilpatrick ES, Keevil BG, Jagger C, Spooner RJ and Small M. Determinants of raised C-reactive protein concentration in type 1 diabetes. **QJM.** 2000; 93(4): 231-6.
63. Forsblom C, Moran J, Harjutsalo V, Loughman T, Waden J, Tolonen N, Thorn L, Saraheimo M, Gordin D, Groop PH and Thomas MC. Added Value of Soluble Tumor Necrosis Factor Alpha Receptor-1 as a Biomarker of ESRD Risk in Patients With Type 1 Diabetes. **Diabetes Care.** 2014.
64. Volpe CM, Abreu LF, Gomes PS, Gonzaga RM, Veloso CA and Nogueira-Machado JA. The production of nitric oxide, IL-6, and TNF-alpha in palmitate-stimulated PBMNCs is

enhanced through hyperglycemia in diabetes. **Oxid Med Cell Longev.** 2014; 479-587.

65. Fisman EZ and Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? **Cardiovasc Diabetol.** 2014; 13(1): 103.
66. Guerre-Millo M. Adiponectin: an update. **Diabetes Metab.** 2008; 34(1): 12-8.
67. Han Y, Zheng YL, Fan YP, Liu MH, Lu XY and Tao Q. Association of adiponectin gene polymorphism 45TG with gestational diabetes mellitus diagnosed on the new IADPSG criteria, plasma adiponectin levels and adverse pregnancy outcomes. **Clin Exp Med.** 2014.
68. Li J, Su S and Zong X. Analysis of the association between adiponectin, adiponectin receptor 1 and diabetic cardiomyopathy. **Exp Ther Med.** 2014; 7(4): 1023-1027.
69. Arikoglu H, Ozdemir H, Kaya DE, Ipekci SH, Arslan A, Kayis SA and Gonen MS. The Adiponectin variants contribute to the genetic background of type 2 diabetes in Turkish population. **Gene.** 2014; 534(1):10-6.
70. Guo Y, Yu W, Sun D, Wang J, Li C, Zhang R, Babcock SA, Li Y, Liu M, Ma M, Shen M, Zeng C, Li N, He W, Zou Q, Zhang Y and Wang H. A novel protective mechanism for mitochondrial aldehyde dehydrogenase (ALDH2) in type 1 diabetes-induced cardiac dysfunction: Role of AMPK-regulated autophagy. **Biochim Biophys Acta.** 2014; S0925-4439(14)00145-8.
71. Lin JT, Chen HM, Chiu CH, Liang YJ. AMP-activated protein kinase activators in diabetic ulcers: from animal studies to Phase II drugs under investigation. **Expert Opin Investig Drugs.** 2014; 26: 1-13.
72. Uusitupa MI, Niskanen L, Luoma J, Vilja P, Mercuri M, Rauramaa R, Yla-Herttuala S. Autoantibodies against oxidized LDL do not predict atherosclerotic vascular disease in non-insulin dependent diabetes mellitus. **Arterioscler Thromb Vasc Biol.** 1996; 16(10): 1236-42.
73. Rodriguez-Segade S, Camina MF, Paz JM and Del Rio R. Abnormal serum immunoglobulin concentrations in patients with diabetes mellitus. **Clin Chim Acta.** 1991; 16; 203(2-3): 135-42.
74. Petersen JS, Kulmala P, Clausen JT, Knip M and Dyrberg T. Progression to type 1 diabetes is associated with a change in the immunoglobulin isotype profile of autoantibodies to glutamic acid decarboxylase (GAD65). Childhood Diabetes in Finland Study Group. **ClinImmunol.** 1999; 90(2): 276-81.
75. Choi YH, McKeown RE, Mayer-Davis EJ, Liese AD, Song KB and Merchant AT. Serum C - reactive protein and Immunoglobulin G Antibodies to Periodontal Pathogens may be Effect Modifiers of Periodontitis and Hyperglycemia. **J Periodontol.** 2014.
76. Jennbacken K, Stahlman S, Grahnemo L, Wiklund O and FogelstrandL. Glucose impairs B-1 cell function in diabetes. **Clin ExpImmunol.** 2013; 174(1): 129-38.
77. Svensson J, Eising S, Mortensen HB, Christiansen M, Laursen I, Lernmark A, Nilsson A, Simonsen LB, Carstensen B, Pociot F, Johannesen J and Danish. High levels of immunoglobulin E and a continuous increase in immunoglobulin G and immunoglobulin M by age in children with newly diagnosed type 1 diabetes. **Hum Immunol.** 2012; 73(1): 17-25.
78. Virella G, Carter RE, Saad A, Crosswell EG, Game BA and Lopes-Virella MF. Distribution of IgM and IgG antibodies to oxidized LDL in immune complexes isolated from patients with type 1diabetes and its relationship with nephropathy. **Clin Immunol.** 2008; 127(3): 394-400.
79. Cojocaru M, Cheta N, Cheta DM, Cojocaru IM and Farcaşiu E.The effect of magnesium deficit on serum immunoglobulin concentrations in type 1 diabetes mellitus. **Rom J Intern Med.** 2006; 44(1): 61-7.
80. Zhao JB, Mikata A and Azuma K. Immunoglobulin deposits in diabetic microangiopathy. Observations in autopsy materials. **Acta Pathol Jpn.** 1990; 40(10):729-34.