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Review Article

Immune Dysfunction in Diabetes Mellitus (DM)

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ABSTRACT

Diabetes mellitus patients are more prone to infection and also the wound healing capacity is very less. As the immune cells are well established mechanisms to protect us from pathogens. So, this article tried to combine all the recent updates of the relevant scientific data that have been done till now on "The effect of diabetes mellitus on the immune cells". It has been well described that there is no or less effect of diabetes mellitus on the adaptive immune system. But if it comes to innate immune system diabetic mellitus affects the cellular functions like chemotaxis, phagocytosis, and killing of pathogens by monocytes, macrophages, and neutrophils. Most studies showed that decrease in normal cellular function, and alteration in enzyme activity and cytokine secretion in diabetic monocytes, macrophages, and neutrophils when compared to control cells. Improvement in cellular functions can be achieved by controlling diabetes mellitus. By understanding how the immune cells were altered in diabetes mellitus further we can proceed by targeting therapeutically to achieve better results in regulation of diabetic complication and improve the lifespan of diabetic patients.

Key words: Hyperglycemia, Insulin, Monocytes, Macrophages, Neutrophils, Advanced Glycation end product (AGE)

INTRODUCTION

Immune and metabolic systems are interrelated and most fundamental requirement for survival. Diabetes mellitus (DM) is a clinical syndrome associated with metabolic disorder due to impairment in insulin secretion or its action leads to hyperglycemia. Estimated worldwide diabetics deaths are 4.6 million per year. (Espinoza-Jim&#xe9 et al. 2012).In future by 2030, it would reach 525 million. These statistics alert the whole world to focus on diabetes.(Xiu et al. 2014).Further Long term complication and immune compromise arise in hyperglycemia condition (11.2mmol/l or 220 mg/dl)(Boyanova and Mitov 2013) cause many problems in DM like atherosclerosis, nephropathy, neuropathy,(Gyurko et al. 2006).It also has a role in other diseases like rheumatoid arthritis, osteoporosis, aging(Singh et al. 2014) through hyperosmolarity, diacylglycerol, protein kinase C(PKC) activation and oxidant formation (Ceolotto et al. 2001). Complications in diabetes are mainly caused by chronically elevated inflammatory immunity as the major cause of morbidity and mortality of diabetic patients (Sun et al. 2012). There may not be any direct alteration in the adaptive immunity, but whereas in innate immunity, there is an alteration in its functions like cytokine response, chemotaxis, phagocytosis, and killing. (Xiu et al. 2014) Virulence of microbes increases in hyperglycemia and its increased microbial adherence in diabetic while comparing with nondiabetic or normal cells. Ex;-candida Albicans (opportunistic pathogen) Also Surgical site infection by staphylococcus aureus is also frequently occurred as a serious complication in diabetes. (Yano et al. 2012) due to alteration in immune cell function (Geerlings and Hoepelman

1999).These infectious complications have more effect on diabetic prognosis (Yates et al. 2009). In this respect diabetes considered worldwide as a secondary immune deficiency next to malnutrition (Daoud et al. 2009).

As indicated above only innate immune cells function is altered in hyperglycemia, so among the innate immunity cell major role was played by, monocytes, macrophages, and neutrophils. As all these are originated from the same precursor they have some common features (V. Kumar and Sharma 2010). Interestingly the approach of the

Ongoing studies worldwide are not solely on examining the role of altered immune cells in cause of disease but it should also need to focus on the diabetic phenotypic effect on the immune system itself (Daoud et al. 2009).

Initially, when there is an injury, neutrophils will invade first to the site of injury to execute foreign particles and secrete cytokines (Henderson et al. 2003). These cytokines recruit monocytes along with neutrophils and macrophages (Petrofsky and Bermudez 1999). These cytokines also stimulate pro-inflammatory and anti- inflammatory responses (Duffield 2003) (Rao, Zhong, and Sun 2014). Mice infected with pathogenic bacteria like non-typhoidal Salmonella, Shigella, and Vibrio parahaemolyticus shows high mortality morbidity and bacterial load in streptozocin-induced hyperglycemic mice than normal (Koley et al.2016). Hyperglycemia activated leukocytes are also involved in insulin resistance in T2D (de Vries et al. 2015).

In this paper, we intend to review recent updates of the action of immunological cells particularly monocytes, macrophages and neutrophils in diabetes. These cells generate cytokines and reactive oxygen species (ROS) as the hallmark of many diseases which are linked to metabolic and vascular disorder like diabetes are caused by oxidative stress due to free radicle (Wiernsperger 2003). Which has intense effect on glucose consumption, utilization and on its counter hormone insulin, glucagon.

1. Immune Cells in Hyperglycaemia

1.1 Monocytes:

Monocytes are developed in the bone marrow from the myeloid progenitor cells and migrate to peripheral blood to reach specified tissue (Volkman and Gowans 1965).They have a very short lifespan and travel in blood for approximately 10-20 hr. before entering into tissue.(Sunderkötter et al. 2004).

i. TNF-α and its pathways:-

Monocytes and macrophages from humans and mice of type 1 diabetes (TID) express high levels of enzyme long-chain acyl-CoA synthetase 1(ACSL 1) catalyzes the thioesterification of fatty acids through increased release of PGE2 (prostaglandin E2)(Kanter et al. 2012) . In monocytes, CD33, a membrane receptor has the ability to inhibit the cytokine production through its immunoreceptor tyrosine-based inhibitory motif (ITIM). Ex vivo studies on T2D patient's monocytes suggest that there is CD33 down-regulation and suppressor of cytokine signaling protein-3 SOCS-3 upregulation, whereas high expression levels of IL-8, TNF-α, IL-12p70 via ROS.(Gonzalez et al. 2012).

Monocytic THP-1 cells and human PBMC, results in high level (2 to 5 fold) mRNA expression of cytokines TNF-α,IL1-β, and their receptors(TNFR,IL-1R) CD27L,monocyte chemoattractant protein-1 (MCP-1) and inflammatory chemotactic gene inducible protein-10 (IP-10),β2-integrins and some metalloproteinase in High Glucose than Normal Glucose. The highest level of gene expression is shown in IL-12. Also proved that these are under the control of pathways protein kinase C (PKC), p38 MAPK (p38), c- Jun-terminal kinase, and inhibitory kappa B kinase (Wen et al. 2006) In another study on THP-1 monocytic cells also showed rise in expression levels of monocyte chemoattractant protein-1 (MCP-1), TNF-α, β (2)-integrin, interleukin-1β. Along with increase of transcription in

MCP-1 gene and protein level and adhesion of THP-1 to endothelial. Specific inhibitors of oxidant stress, protein kinase C, ERK1/2, and p38 MAPK blocked the elevated levels of MCP-1 by HG (Shanmugam et al. 2003)

PGE2 and cytokine secretion of monocytes has been regulated by the Extracellular signal-regulated protein kinases (ERK) pathway, is further activated by mitogen-activated protein kinase (MEPK or MEK) tyrosine and threonine phosphorylation and inactivated by mitogen-activated protein phosphatase-1 (MPK-1) dephosphorylation. Ceolotto et al in-vivo in human monocyte experimental results clearly shown that there is significant increase in the activity of the ERK and MEK kinases but not in the MPK-1 in hyperglycemia it has a negative role in pathophysiology of monocyte and macrophages As most of them are under NF-kB control so as expected there is upregulated in NF-kB expression levels (Ceolotto et al. 2001)

IL-6 in intermediate monocytes and its controversy:-

When healthy individuals are induced acute hyperglycemia by IV infusion of dextrose and octreotide for 2 hr. Results in a decrease of IL-6 expression. Where as In vitro results of PBMC with high glucose also showed reduction in IL-6 and IL-17A expression levels. Among them, intermediate monocytes show highest reduction. The path ways for the reduction of IL-6 was identified as P38 MAPK expression not by phosphorylation using as electro chemiluminescence assay and SB203580 inhibitor (Spindler et al. 2016). CD16+ CD14+ is intermediate monocytes which are more in T2D and secrets pro-inflammatory cytokines TNF-α and IL-1 β. (Terasawa et al. 2015)

The in vivo study on normal and well (HbA1c $\leq$ 6.5) or poorly (HbA1c > 6.5) controlled DM patients showed that monocyte chemoattractant protein (MCP-1) and IL-6 are upregulated, in diabetic patients than healthy subjects.. So control of glycaemia might decrease only IL-6 expression .In-vitro studies on monocytes also showed same results as in vivo. (Bernal-Lopez et al. 2013)

Monocytes towards atherosclerosis:-

Lipopolysaccharide (LPS) activated monocytes from T1D patient's exhibits reduction in IL-6 and CCL2 secretion. These cytokines are induced through MAPK/ ERK and P38 pathways. So LPS is acting somewhere in these pathways. Apolipoprotein E (Apo E) is effective in protection of monocytes from lipid accumulation is also altered in monocyte. (Wehrwein et al. 2006) In hyperglycemia the HUVE, showed increased expression of protein and mRNA levels of CCL5 and also increased monocyte adhesion (2.1-2.2 fold) through the P38 MAPK pathway. (Gao et al. 2015)

Human monocytic cells when exposed to high glucose enhanced the secretion of resistin and TNF- α mRNA and protein levels.(Tsiotra et al. 2013). HG and PIT-1 decrease expression of PIP3 and at the same time there is an increase in the concentration of ICAM (intercellular adhesion molecule 1) in HUVEC and CD11a (lymphocyte function- associated antigen 1, LFA-1 subunit) in monocytes.(Manna and Jain 2014)

ii. Insulin resistance by hyperglycemia:-

Studies on circulating monocytes of hyperglycemic patients reveal that there is high expression level of CD11c and lower expression levels of CD206 with respect to normal glycemic control monocytes.CD11c elevation correlates with increase insulin resistance, obesity, triglyceridemia and low serum IL-10. They might undergo M1 inflammatory polarization in high glucose condition (Torres-Castro et al. 2016).

Taken together, all the above studies have investigated the effect of hyperglycaemia on monocytes. It was clearly evident that there is an effect of cytokines on the proper functioning of monocytes and its role in inflammation, proliferation, and adhesion leads to other complications like cardiovascular diseases

atherosclerosis. But there are some controversies in IL-6 upon which future research has to be concentrated.

1.2 Macrophages:-

Macrophages derived from monocytes of myeloid progenitor cells in bone marrow have a crucial role in immune response and homeostasis i.e. immune regulation, host defense and wound healing(Xiu et al. 2014) (Rosenberger and Finlay 2003). Are involved in the first line of defense (Laskin et al. 2011) Those are broadly classified into classically activated macrophages and alternatively activated macrophages ((Espinoza- Jim&#xe9 et al. 2012).These both cells have opposite action and have a major role in type 1 and type 2 diabetes. i.e. islet cell destruction (Kolb-Bachofen and Kolb 1989) Microvascular and atherosclerotic lesions ((Ross 1993). Substantial increase in tissue macrophages is a common feature in all complications nephropathy, atherosclerosis, neuropathy, retinopathy (Sun et al. 2012). The common progenitor cells monocytes after they enter into tissue compartments differentiated irreversible into macrophages. These resident macrophages exhibit phenotypic differences from recruited macrophages. Resident macrophages differ in their morphology and function as they express germline encode nonclonal receptors most studies of macrophages are on (PEMs) peritoneal exudate macrophages and (SPMs) splenic macrophages because PEMs are easy to isolate and SPMs have heterogeneous population and have immune-modulatory effect (G. Liu et al. 2006).

i. Proliferation:-

The proliferation of the splenic macrophage (SPMs) and WEHI -3 cell lines are more in the hyperglycemic environment but not by osmolality. (5.6-30mM). It is concentration dependent in the presence of CSF-1 (Y. J. Liu et al. 1995).The Colony stimulating factor (CSF-1) enhances the proliferation and growth of mouse splenic macrophages as its CSF-1receptor (CSF-1r) expression levels have three-fold increase in hyperglycaemia or DM. The infiltration of macrophages might be due to the growth and proliferations are the cause for a diabetic lesion (Saini et al. 1996). Along with hyperglycaemia, hyperlipidemia has synergistic effect in stimulation of isolated macrophage proliferation and accumulation of macrophages in atherosclerotic lesions by ERK-mediated LDL oxidation glucose pathway (Lamharzi et al. 2004).

ii. Epigenetic alterations and IL-6:-

In vitro studies, hyperglycaemia leads to macrophage dysfunctioning on long-term exposure. Also significant reduction in pro-inflammatory cytokines TNF-α and IL-6 production, CD86 and CD54 expression but enhanced nitric oxide (NO) secretion in F4/80(+) peritoneal exudate macrophages (PEMs) When treated with IFN-γ and LPS from streptozotocin (STZ) induced mice with diabetes for 4 month. A similar change was shown in bone marrow derived macrophages indicates that there is involvement of epigenetic alterations in macrophage precursors. These results are reversed by AKT and ERK inhibitors (Sun et al. 2012).

Studies on the effect of epigenetic histone modification on the inflammatory cytokine production by THP-1 derived macrophages in hyperglycaemia, reveals that inhibition of specific H3K9me3 methyltransferase SUV39H1 by chaetocin in high glucose treated macrophages increases the expression levels of inflammatory cytokines interleukin-6 (IL-6), IL-12p40, macrophage inflammatory protein-1α (MIP-1α), and MIP-1β. Contrarily when High glucose treated macrophages under over expression of SUV39H1 also increases the expression levels inflammatory cytokines.(Li et al. 2016)

So as a result of these experimental data the macrophage alteration by AKT/ERK pathway and epigenetic histone modification might be one of the mechanisms for alteration in inflammatory cytokine secretion.

iii. Islet cell destruction:-

The PEM as a source of inflammatory cytokines shown highest expression level for IL-12 (5.4 fold) in time (3-12h) and dose-dependent manner (10, 17.5, 25 mmoles/liter). IL-12 protein accumulation and its mRNA expression (20 fold change) from mouse peritoneal macrophages (MPM) is also increased in high glucose in streptozotocin-induced type 1 diabetic mice as well as type 2 diabetic db/db mice. These IL-12 signals T-cell to become Th1 cell. Both Th1 and IL-12 cell infiltration is vital importance in autoimmune diabetes and inflammation, interestingly research on mouse proved that reduction in IL-12 can reduce atherosclerosis and inflammatory complications (Wen et al. 2006) As the protein kinase C, p38 MAPK (p38), c-Jun-terminal kinase, and inhibitory-kappa B kinase activity were increased in MPM in the presence of HG. Also, the inhibitors of these pathways reduce the HG-induced IL-12 expression in MPM. So it is expected that these pathways are involved in HG-induced IL-12 gene expression in streptozotocin (STZ) induced type I diabetic mice and type II diabetic db/db mice. The IL-12 has a major role in diabetic inflammations (Wen et al. 2006). The study on P38 MAPK activity in monocytes isolated from metabolic syndrome patients show that MAPK could a promising target to prevent diabetic complication. (Jialal, Adams- Huet, and Pahwa 2016)

IL-27 has a β cell protection activity in diabetes was concluded based on result that Islets proinsulin levels were lower where as The islet infiltration by F4/80(+) CD11c (-) 7/4(-) macrophages, CD4 (+) T cells, and CD8 (+) T cells was increased in EBI3 (-/-) and WSX-1(-/-) mice compared with WT mice, but after recombinant IL-27 administration these all results are reversed and also there is an increase in islet proinsulin levels in WT and EBI3(-/-) mice.(Fujimoto et al. 2011)

iv. Microbicide property:-

The isolated peritoneal macrophages from streptozotocin-induced hyperglycemic mice show a low level of bacterial killing and phagocytosis than normal mice infected with pathogenic bacteria like non-typhoidal Salmonella, Shigella, and Vibrio parahaemolyticus. So as a result of a disturbance of the innate immune function in the hyperglycemic mice might make diabetic individuals more prone to bacterial infection. (Koley et al. 2016)

v. Atherosclerosis:-

Studies on RhoA/ROCK activation of the macrophages by hyperglycaemia using RAW 264.7 cell line in atherogenesis reveal that this RhoA/ROCK activation follows the JNK/ERK pathway but not through NF-kB pathway by using ROCK inhibitor hydroxyl fasudil and Si RNA silencing. As a result of macrophage activation releases more pro-inflammatory phenotypes.(Cheng et al. 2015). Accumulation of cholesterol in arterial macrophage is one of the causes for atherosclerosis in diabetes. This cholesterol transport was mediated by ATP- binding cassette transporter A1 (ABCA1) is the roprotective protein. Their results showed that high glucose activates ERK pathway and produce ROS. These generated ROS involved in degradation of ATP-binding cassette transporter A1 (ABCA1) mRNA and protein level (Chang et al. 2013) (Spartano et al. 2014).

RAW264.7 macrophages when stimulated with high glucose (15-25mM) along with LPS and normal glucose (5mM) with LPS. High glucose alone can't able to induce NO generation and cytokine release. But in combination with LPS, high glucose induce NO generation by inducible nitric oxide synthase (iNOS) expression and IL-1 β secretion at a higher rate than in normal glucose. it was through increased phosphorylation levels of protein kinase C-α (PKC-α), protein kinase C-delta (PKC-δ), and p38 phosphorylation and NF-κB transcriptional activity lead to inflammation

and atherosclerosis in diabetes.(Hua et al. 2012).

vi. M1 polarization:-

Primary monocytes from healthy donors were differentiated into macrophages and exposed to normal glucose, high glucose, and high mannitol as osmotic pressure control. The results showed that high glucose macrophages have high expression levels of CD11c and nitric oxide synthase (NOS) whereas downregulation of IL-10 and arginase -1 in comparison with normal glucose and osmotic pressure control. As a result it was concluded that high glucose has an effect on macrophages leads to M1-like inflammatory polarization in diabetes. (Torres-Castro et al. 2016)

In summary from the above studies, it was clear that there is a well-established effect of hyperglycaemia on the macrophage functional activity and phagocytosis through different pathways. But further studies has to focus on understand and identify downstream signals which lead to different pathways and how the pathways are interrelated. This will give us the better approach to understanding the mechanism and develop therapeutic target for cure or at least decrease disease progression and complications.

1.3 Neutrophil:-

Elie Metchnikoff discovered neutrophils in starfish larva while conducting studies on inflammation. These cells are the first line of defense and act first.(V. Kumar and Sharma 2010) .Among the blood leucocytes 60-70% are granulocytes and among the granulocytes 90% are neutrophils. The largest fraction of white blood cells (WBC) is polymorphonuclear neutrophils (PMN) (Walrand et al. 2006). Bone marrow is the places where the neutrophils originate from the pluripotent stem cells attain maturity within 8-10days. Functional properties of neutrophils include granular content, degranulation, adhesion, aggregation, phagocytosis, chemotaxis and respiratory burst activity (Bogomolski-Yahalom and Matzner 1995)

Due to inflammation, there is significant increase in IL-6 (2.9fold), chemokines response (KC 2.6 fold, MCP-1 2.6 fold, MIP-1α 4.4 fold) and superoxide release by cytochrome c reduction where as reduced chemotaxis towards FMLP and WKYMVm in Akita PMN(novel model for hyperglycaemia) over wild type PMN. Many of this function are linked with NADPH oxidase and myeloperoxidase enzyme (MPO) involving metabolic pathways. Polymorphonuclear neutrophils (PMN) damage tissue directly by superoxide protease, nitric oxide (NO) release and indirectly by TNF and IL-1 in inflammation. (Gyurko et al.2006).

i. NADPH complex:-

Superoxide production in polymorphonuclear neutrophils (PMN) is by the action of NADPH oxidase. It is made up of membrane-bound (gp91phox and p22phox) and cytoplasmic (p47phox, p67phox, and rac) components. Phosphorylation of p47phox and its translocation and assembly leads to NADPH oxidase activation. There is a pre-maturation and translocation of cytoplasmic p47phox in neutrophils proves that the NADPH oxidase activity is more in diabetic neutrophils (Gyurko et al. 2006).

ii. NADPH action:-

The NADPH oxidase is thought to be the reason for the release of ROS by the activity called oxidative burst. Its action on molecular oxygen generates superoxide anion O2-. Further this anion form into hydrogen peroxide (H2O2), hypochlorous acid (HOCL) and MPO are principle enzymes produced inside the neutrophil azurophilic granules. Interestingly the results showed high MPO protein expression level whereas decrease in MPO activity measured by HOCL production in diabetic neutrophils when compared to control. C.albicans phagocytosis activity was measured by May-Grunwald-Giemsa staining showed lower in diabetic than control. These indicate the importance of HOCL production in MPO activity in the

killing and phagocytosis function of neutrophils (de Souza Ferreira et al. 2012a).

iii. MPO action:-

ROS is a measure of neutrophil activation and phagocytosis. MPO catalyze H2O2 to HOCL, as its expression is more in type II diabetes (T2D) might make them more prone to cardiovascular disease. It was clearly evident when elevated MPO plasma levels are observed in cardio syndrome patients (de Souza Ferreira et al.2012a).While evaluating the expression levels of MPO by measuring HOCL formation, surprisingly MPO mRNA and protein expression levels are high but HOCL generation is decreased in diabetic neutrophic ls when comparing control (de Souza Ferreira et al. 2012a).The reduced HOCL formation is thought to be due to alteration in the enzymatic activity of MPO by AGE formation. There is also being a feedback mechanism on enzyme activity and concentration. As HOCL is an important member of ROS it causes problem in pathogen immune system (de Souza Ferreira et al. 2012a).

iv. NET and its Microbicide action:-

Along with phagocytosis neutrophils are endowed with the special ability to generate extracellular trap called neutrophil extracellular trap (NET)(Joshi et al. 2013).NET is constitutes of granule proteins and chromatin to kill pathogens(Brinkmann et al. 2004).NET releases after the cell membrane breaks which depends on the generation of ROS by NADPH oxidase. Chronic granulomatous disease patients have NADPH gene mutation so they can't be able to form NET. These NET provide a microbicidal property to neutrophils (Fuchs et al. 2007).As H2O2 is a substrate for MPO which is produced from the superoxide generated by the NADPH oxidase system so deficiency and dysfunction of MPO have a mild to moderate effect on NET formation. They observed the failure of NET formation in MPO-deficient donor patient's neutrophils. Whereas the results of partial MPO-deficient donor make NET Delay in NET formation is seen in pharmacological inhibition of MPO. So MPO has a crucial role in the NET formation and its deficiency make subject prone to candida Albicans infection (Metzler et al.2011). When neutrophilic cells were treated with 0, 5,25mM of glucose and 25 mM mannitol are analyzed by immunostaining for DNA, chromatin, and elastases. The NETs release was quantified by Hoechst 33342. It indicated that high glucose (25mM) has more circulating markers of NETosis and NET release when compared to mannitol (25mM) and normal. Plasma elastase, mono- and oligonucleosome and dsDNA levels are high in T2D than a normal non-diabetic. (Menegazzo et al. 2015)

Neutrophil count is decreased in T1D patients. So as to access the mechanism how the count is decreasing in diabetes. They analyze the protein levels and enzyme activity of neutrophil elastase (NE) and proteinase 3(PR3) both are neutrophil serine proteases present in neutrophil granules. Their study showed that the NE and PR3 levels are more in progressive increases with the more number and titer of antibody against the beta cell antigen. These results are correlated with the elevated level of NET and reduced levels of endogenous serine protease inhibitor α- antitrypsin in T1D. As a result, these might act sensitive biomarkers for T1D at an early stage.(Wang et al.2014)

v. Role of RAC2 in NET formation:-

The null Rac2 mice show less production of ROS and NO leads to failure in NET formation. It was confirmed by the supply of external ROS sources and L-NAME for NO inhibition. As the Rac2 is involved in ROS production The formation of NET essentially needs Rac2 as important component via pathways involving ROS and NO production was assessed in mouse Rac1null and Rac2 null neutrophils with wild-type neutrophils (Lim et al.
2011). The FcR/rac system depends on NADPH oxidized system and increase TNF-α production. So diabetic hyperglycaemia affects both phagocytic and cidal activity of neutrophils (de Souza Ferreira et al. 2012b)

this rac and Cdc42 activate JNK and P38 MAPK pathway (Caron and Hall 1998)

vi. Pathways and delayed response:-

As the pathways are affected during hyperglycaemia, DM patients are more susceptible to infection. The neutrophils NET formation and microbicidal activity are reduced in diabetes than normal. Neutrophils from T2D show high-level expression of IL-6 are responsible for continuous active state which makes them less response to LPS stimuli for long time. It might also be by negative feedback mechanism of NET formation in diabetic neutrophils (Joshi et al. 2013). Diabetic rat peritoneal neutrophils exhibit delayed response when compared to normal might be due to expose to chronic hyperglycaemia for 30days or may be continuous exposure to hyperglycaemia makes them less stimulus(de Souza Ferreira et al. 2012b).

Neutrophils when pretreatment with PKCα/β inhibitor Go6976 or GF109203X decrease NF-kB, TNF-α, production and prevent LPS induced phosphorylation of IKK αe /β, IkB- α, NF-kB and observed failure of activating P38 and JNK pathways. These data strongly supported interconnection of pathways and cytokine production in neutrophil (Wen et al. 2006). Peripheral blood mononuclear cells (PBMC) of diabetic patients have decreased stimulation response with mitogens concanavalin a, phytohemagglutinin, pokeweed mitogen when compared with healthy control patients. Also decrease in diabetic neutrophils, polymorphonuclear cells (PMNC) respiratory burst activity compared to normal. This effect might be due to long-term in-vivo exposure to hyperglycaemia (Daoud et al. 2009).

Calcium dependent processes such as phagocytosis and chemotaxis of neutrophil and lymphocytes are active in protection against microbial infections. While investigating the process of calcium mobilization under the effect of N-formyl-methionyl-leucyl-phenylalanine (f MLP), Thapsigargin (TG), and hydrogen peroxide (H_2O_2) on [Ca^{2+}] (i) homeostasis in neutrophils and lymphocytes isolated from T2D patient's blood. The results showed that there is a decrease in calcium mobilization in T2D than normal. So this calcium mobilization alteration in immune cells might be one of the mechanisms of immune disturbance in diabetes (Kappala et al. 2014)

vii. Synergistic effect of dyslipidemia:-

Neutrophils or PBMC (peripheral blood mononuclear cells) when treated with RHQ (rhodamine-quinoline based chemodosimeter) for measuring endogenous ROS and HOCL. The results showed that HOCL and ROS generation is more in diabetic dyslipidemia neutrophils than diabetic nondyslipidemia neutrophils and normal control. Due to more production of H2O2 and hyperactivity of myeloperoxidase enzyme (MPO) in diabetic dyslipidemia. These results prove that dyslipidemia has a synergistic effect on the generation of ROS and provoke diabetic patients into more complications (Ghoshal et al. 2016).

viii. Proteins and complications:-

Glycated hemoglobin (HbA1c) proportionally elevates the basal ROS production in post menopause females. As the neutrophil function is decreased they may be more susceptible to infection. So glycemic control is more important in post menopause females to prevent diabetic complications.(Saito et al. 2013). Hyperglycaemia elevates the rate of myelopoies is makes the diabetic patients more prone to atherosclerosis. As measured plasma levels of neutrophil produced S100A8/S100A9 is proportionately increased with leukocyte counts in coronary artery disease (Nagareddy et al. 2013). An increase in the activities and its percentage equivalence of neutrophil membrane-bound elastase (MLE), membrane-bound form of cathepsin B (MCB) and their respective intracellular proteases (ICE,ICB) of neutrophils is observed in T2D compared to normal might have a role in diabetic complications (Zurawska-Płaksej et al., 2014).

Studies on human chitinases and chitinase-like proteins i.e. neutrophil-derived chitotriosidase (CHIT1), acidic mammalian chitinase (AMCase) and chitinase 3-like protein 1 (YKL-40) of whole blood isolated neutrophils in T2D. It showed that these levels are high in diabetes than normal. As a token of support, insulin treatment also reverses the protein level (Żurawska-Płaksej et al. 2015). In human CXCR1 and CXCR2 are homologous proteins bind to ELR+ chemokine play a crucial role of functional activities like migration and ROS production in neutrophils. A non-obese diabetes mouse (NOD) is a model for T1D.they found a decrease in CXCR1 mRNA level and its CXCR1 promoter activity in neutrophils from NOD mice. So there is a chance for its contribution in T1D complications. (Haurogné et al. 2015).

From the above data, it was clearly evident that hyperglycaemia alters many of the normal functions and cytokine secretions of neutrophils. In many of the results they just show the correlation with hyperglycaemia. So in future, we have to identify the pathways and its downstream targets for a better therapeutic approach towards complications in diabetes.

2. Insulin and Immune Cells

Insulin is a therapeutically important hormone for treatment and regulation of glucose in diabetes. (Verhagen et al. 2011) It is essentially required to maintain metabolic homeostasis. Initially, insulin bind to its receptor present on the immune cell surface to exhibit its action i.e. Monocytes, macrophages, and neutrophils Insulin mainly activates PI3K-AKT/PKB pathway and ras/MAPK pathway extends its effects like decrease glucose levels (Xiu et al. 2014) (Defronzo et al. 1978).(Xiu et al. 2014).

Insulin resistance arise studies so far conducted on the insulin resistance concluded that it may be due to low-level inflammation in innate immunity mediated by pattern recognition receptors (PPR)(Shiny et al. 2013). People with insulin resistance had been reporting of suffering from coronary risk factors like hypertension, obesity, dyslipidemia and glucose intolerance are major causes of death.(Reaven 1988) (Zavaroni et al. 1989) (Kaplan NM 1989). Nowadays diabetes and atherosclerosis have been closely related and considered as a chronic inflammatory disease (Menu et al. 2012). All types of white blood cells including granulocytes lymphocytes and monocytes are associated with insulin resistance but in beta cell destruction only granulocytes and lymphocytes have a role (Lee et al. 2014).

2.1 Monocytes:

THP-1 is the human myeloid cell line is the best model system for mimic monocyte and macrophage for metabolic syndrome studies like diabetes. (Naderi et al. 2014) Isolated peripheral blood monocytes are sensitive to insulin (The wissen et al. 2014). Insulin internalization study on human circulating monocytes by 125I revealed that the process is energy and temperature dependent. The type II diabetic patient monocytes have decreased insulin internalization ability when compared to normal. It may have a role in insulin resistance to cells in Type II diabetic patients (Trischitta et al. 1986).

i. Proliferation:-

Insulin stimulates proliferation of THP-1 cell line up on 24h treatment. But the effect of stimulation reduced in longer time exposure. It affects morphology and adherence and has a pro-inflammatory effect on monocyte proliferation (Naderi et al. 2014). When human monocytic cells treated with high insulin leads to increased expression levels of resistin and proinflammatory cytokines like TNF- α, IL-6 and Il-1 β might have a role in insulin sensitivity related complications (Tsiotra et al. 2013).

ii. Insulin resistance:-

In females when monocytes are isolated after the intense to moderate exercise. The M1 marker expression is suppressed and the M2 marker MCP-1

expression levels are enhanced. Similarly the serum PPAR-γ target gene CD36 and its activity increases. So exercise has a positive effect in control the inflammatory complication and reduces insulin resistance somehow through PPAR-γ in diabetes specially T2D (Ruffino et al. 2016). Human PBMC are used to evaluate the receptor expression levels in correlation with C-reactive protein (CRP) and inflammatory cytokines involved in insulin resistance. Surprising the IL-6 and TNF – α levels is more and also enhanced P2X7 receptor expression along with high CRP in T2D monocytes than health (Hong Wu et al. 2015, 7).

Monocytes migration is the main reason for inflammation in atherosclerosis. Out of glucose, insulin, and insulin-like growth factor only insulin has an effect on THP-1 monocytic and bone marrow derived monocytic cells migration (BDMC). Pathways studies using pathway inhibitors and surface expression inhibitors concluded that insulin increase surface expression of macrophage-1 antigen (mac-1).which mediates via the Akt pathway for monocyte migration through endothelium, these data suggest the insulin role in atherosclerosis in T2D(S. Y. Jin et al. 2014)

2.2 Macrophages:

i. Atherosclerosis:-

Hyperinsulinemia effects on macrophages make more prone to heart coronary diseases like atherosclerosis. But it was a mystery how insulin involves in the development of atherosclerosis. (Iida et al. 2001) Macrophages interact with acetylated low-density lipoproteins (LDL) through scavenger receptors or acetyl- LDL receptor, degrade them and transform into foam cells involve in atherosclerotic initial stages. These macrophage foam cells are found in atherosclerotic (Steinberg 1997).

The effect of insulin (10-7M) increase the expression level of TNF- α gene and protein release from the monocyte-derived macrophage THP-1 cell. It communicates its activation effect through ERK pathway in MAPK family.. TNF- α increases The release of growth factors and chemotactic proteins of vascular smooth muscle and endothelial cells .i.e. Heparin-binding epidermal growth factors, (VCAM-1) vesicular cell adhesion molecules and metalloproteinase involve in adhesion and migration have a crucial role in atherosclerotic progression.(Iida et al. 2001).

ii. Insulin resistance:-

The adipocyte-derived factor called pigment epithelium- derived factor (PEDF) activates macrophages, through the production of TNF mediates insulin resistance in NOD mice pancreas. Interestingly PEDF inhibitor emetine (emetic) inhibits macrophage activation by PEDF, show attenuation in pancreatic TNF level, insulitis and hyperglycaemia in C57B16 mice, so hopefully as it will show positive results as target in T1D diabetes (Hudson et al. 2016).

2.3 Neutrophils:

These are the nonspecific immune cells recruited as the first line of host defense. These are the cells that respond to inflammation as early as possible and then it communicates with other immune cells. Neutrophils produce proteases among this neutrophil elastase is one to promote the inflammatory response. When hepatocytes treated with neutrophil elastases it leads to inflammation and insulin resistance. After removal of elastase from high-fat diet induced obese mice has less tissue inflammation along with low adipose tissue neutrophil and macrophage content. Implying that it might affect glucose tolerance and insulin resistance specifically in type 2 diabetes (Talukdar et al. 2012).The neutrophil function requires ATP-dependent energy produced by glucose metabolism (Borregaard and Herlin 1982). It was reported that 50% reduction in glycolysis and glucose use in diabetic patients (Munroe and Shipp 1965). As the glycolysis is impaired in diabetes neutrophils due to loss of synthase phosphatase activity it affects neutrophil functional properties (V 1983).

Activin A is a transforming growth factor beta family cytokine has a role in inflammation caused insulin resistance. So this activin A release by TNF-α in insulin deficiency was checked in murine bone marrow derived precursor neutrophils From 8 to 10 weeks old C57BL6/J male mice (Wang et al. 2014). It was concluded that TNF- α stimulated activin A release from the neutrophils. It has to be under control by insulin or it may create inflammatory complications in T2D (Hui Wu et al. 2013).Diabetes was associated with greater blood neutrophil count found in non-Hispanic white HFE C282Y homozygote's (Barton et al. 2016).T2D is associated with insulin resistance (IR) which is due to inflammation. As the Neutrophil lymphocyte ratio (NLR) is the indicator for inflammation. It was proved that there is an increase in the insulin resistance along with the NLR ratio increase. So it provides us a way to make it a marker for insulin resistance (Lou et al. 2015).

3. AGES FORMATION AND EFFECT ON IMMUNE CELLS

In diabetes due to metabolic and functional impairment leads to accumulation of glucose and it's analog. Its fusion with proteins and lipids catalyzed by non-enzymatic reaction leads to a formation of advanced glycation end product (AGE). AGE play a crucial role in long-term complications by altered receptor function, enzymatic activity and disrupt molecular conformation of proteins lipids and sometimes nucleic acid (Singh et al. 2014). AGE quantitatively and qualitatively modifies the extracellular components like laminin, collagen, and vitronectin. It also has an effect on adhesion, matrix accumulation, growth. AGE-modified proteins interact with receptors on the macrophages and endothelial cells to alters their normal functions (M. Brownlee 1992)

3.1 Age Formation and Interaction:

AGE is formed by glycosylation and glycoxidation, at first; it gives rise to reversible Schiff's base later on due to intramolecular rearrangements. It forms Amador product such as glycated hemoglobin which is elevated in diabetes. Further modification by irreversible chemical changes forms AGE. (Michael Brownlee 2001) (Alba- Loureiro et al. 2007). AGE interaction with receptors changes its properties leads to micro and macro vasculature complications as the result of its accumulation, mainly under a hyperglycemic condition as in diabetes. Monocytes are activated by the soluble AGEs and monocyte migration is inhibited by the AGE interaction with basement membrane and their receptor for advanced glycation end products (RAGE). As a result of RAGE activation, there is a transcription factor nuclear factor-B and its target genes upregulation. AGE +RAGE interaction in endothelium increases its permeability, block nitric oxide production and also increases ROS generation. It has also been proved to have an inducing effect on the two oxidized LDL receptors on macrophages i.e.CD36 and macrophages scavenger receptor class A. It makes macrophages to uptake more oxidized LDL and then they transform into foam cells. Which are present more in atherosclerotic lesions ((Goldin et al. 2006) (Alba-Loureiro et al. 2007).

i. AGE on monocytes:-

Earlier studies proved that AGE bind with RAGE generate ROS which triggers cytokine secretion contributes to proliferation and inflammation in cells. Nam et al determine the effect of AGE on the HUVEC and THP-1 co-culture with VSMC results showed that proliferation was induced by the AGE in VSMC along with significant elevation in the cytokine expression like IL-6 and MCP-1(Nam et al. 2011). The AGE didn't have any effect on cell viability but enhance the expression of VCAM-1 and MCP-1 in HUVEC. Whereas AGE with PKC- β inhibitor decreases their expression. So this pathway could be a therapeutic target for AGE-induced Atherosclerotic complication in diabetes. (Rempel et al. 2015)

When examining the effect of AGE or RAGE on (ATP-Binding Cassette Transporter) ABCA1 expression using RAGE ligand S100B along with some other genes like ABCA1, ABCG1, ABCG8 and LXR target genes LXR- α and LXR-beta on THP-1 monocyte cells. The results revealed that ABCA1 protein and mRNA levels are significantly reduced in S100B ligand treatment. This reduction was prevented using anti-RAGE antibody on THP-1 cells. As a support of these results the peripheral blood monocytes (PBMC) from diabetes also showed a reduction in ABCA1 expression. Liver X receptor (LXR) ligand treatment reverses the effects of S100B. So It was concluded that the RAGE can reduce the cholesterol transport mediated by ABCA1 in monocytes which have a role in atherosclerotic complications in diabetes. (P. Kumar et al. 2013)

It was concluded that AGE effect on monocytes induces proliferation and it also decrease cholesterol efflux through ABCA1.future research has to focus on this to find more interesting facts.

ii. AGE on macrophage:-

On incubation with AGE –albumin human macrophage U937 cell line, which has RAGE shown dose- dependent expression of tissue factors (TF). As well as PBMC from normal and diabetic patients treated with AGE –albumin also results in increased expression of tissue factors in diabetes as normal control. Tissue factor expression is thought to be by the involvement of oxidant stress. (Ichikawa et al. 1998) When evaluating the action of AGE on macrophage polarization. It induces the expression of IL-6 and TNF- α in macrophages and also up regulates the M1 markers like iNOS, CD11c, and CD86 whereas M2 markers arg1 and CD206 are not affected or unchanged. It also increases the RAGE expression and NF-kB activation. These results caused by AGE are attenuated by using an anti-RAGE antibody or NF-kB inhibitor PDTC (X. Jin et al. 2015). So as a conclusion the AGE can positively regulate M1 phenotype differentiation via RAGE/NF-kB pathway and mediate serious complications like thrombosis and atherosclerosis through tissue factors in DM.

Heparanase (HPA) devoid of its enzymatic activity it can also phosphorylated some signaling pathways like AKT in macrophages migration pathways in the presence of AGE. In-vitro study using ana-1 macrophages, the HPA protein and mRNA level are significantly high in the presence of AGE. Anti HPA antibody which identified only non-enzymatic terminal pretreatment results in termination of AKT phosphorylation and macrophage migration. LY294002 (PI3k/AKT inhibitor) also prevents migration of macrophages. The anti-RAGE antibody also attenuates AGE-induced HPA expression, AKT phosphorylation and macrophage migration. So these results proved that AKT phosphorylation is one of the pathways for macrophage migration which was mediated by HPA (Qin et al. 2013).

Albumin isolated from T1D patients are used to treat J774 macrophages. While isolating albumin they found glycated modified and carboxyl-methyl-lysine (CML) modified albumins are higher in T1D than control. Also observed the alterations in APOA-1/HDL mediated cholesterol efflux in diabetic albumin treated in comparison with controlled albumin and correlates with a reduction in ABCA-1 protein content. Elevations of intracellular lipids level are observed even in cholesterol acceptor presence. It was correlated with enhanced stearoyl-CoA desaturase-1 expression and reduced expressions of Janus kinase-2 were induced by albumin from T1D patients. This albumin-mediated lipid accumulation and ABCA1 alteration possibly have a role in atherosclerotic complications (Machado-Lima et al. 2013).In glyceraldehydes (inducer of AGE formation) treatment macrophages there is decrease in the efflux of HDL-mediated cholesterol and 7-keto cholesterol in correlation with decreased

expression of ABCA-1 and ABCG-1(Ibarra et al. 2011).

In conclusion AGE on macrophages induce migration, reduce cholesterol efflux, alters pathway, and induces M1 polarization and insulin resistance.

iii. AGE on neutrophils:-

When PMN treated with AGE-HAS the results showed the dose and time-dependent rise in ROS and reactive nitrogen intermediates (RNI) production. It might be via NADPH oxidase and inducible nitric oxide synthase (iNOS). When using inhibitor for both enzymes diphenyleneiodonium, a flavoprotein and also anti-RAGE prevent the rise in ROS and RNI. So the AGE –RAGE interaction via NADPH and iNOS is one cause for oxidative stress and diabetic complications. (Bansal et al. 2012).While accessing the plasma levels of AGEs and their effect on the proteolytic enzymes like cysteine, cathepsin B in plasma and neutrophils in T2D patients. There is a significant rise in AGE formation in diabetic than normal. Also found that AGEs reduces the activity of cathepsin. These AGE related cathepsin activities possibly play a role in diabetic complications. (Grzebyk, Knapik-Kordecka, and Piwowar 2013)

In conclusion, AGE has an effect on neutrophils functional properties. But till now limited data is available regarding the effect of AGE on neutrophils. Hope the ongoing research will provide more data in near feature.

SUMMARY

The immune system is important for protection. In diabetes, hyperglycemia and hyperinsulinemia condition alters the normal functioning properties of the innate immune system but not or very less effect on the adaptive immune system. There is a lot of alteration in immune cellular functions in diabetes mellitus and some of the controversial results might be due to the differences in the experimental procedures, experimental conditions and maintenance time. Still, there is a need for better experimental procedures to get a better understanding how immune cells act in diabetes. The greatest challenge for future scientists to study diabetes is that "a different stage of diabetes has a different effect on immune cells ". Hope future scientists will decode the cause for complications in diabetes and provide the best treatment and improve the lifespan of a diabetic patient.

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ABBREVIATIONS

DM-diabetes Mellitus
TID-type 1 diabetes
T2D-type 2 diabetes
ERK-extracellular signal-regulated protein kinase
MAPK-mitogen-activated protein kinase
MPK-1-mitogen-activated protein phosphatase-1
PKC-protein kinase C
PBMC-peripheral blood mononuclear cells
LPS-lipopolysaccharide
NET-neutrophil extracellular trap
PMN-polymorph nuclear neutrophils
HUVEC-human umbilical vein endothelial cells
ROS-reactive oxygen species
PEM-peripheral exudates macrophages
SPM-splenic macrophages
AGE-advanced glycation endproduct

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