

## Avoiding cardiovascular disease in type1 and type2 Diabetes Mellitus by targeting the coagulatory Alterations–A Systematic Review

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### Abstract

Earlier we have already evaluated in detail the initiation of atherosclerosis in both type1 diabetes mellitus (T1DM) as well as type2 diabetes mellitus (T2DM) and details of acetylation end-glycation-products (AGE), receptor for AGE (RAGE) role of neutrophil extracellular trap formation and influence on cardiovascular disease (CVD). Further we reviewed how CVD is avoided with better Sodium Glucose Transporter 2 (SGLT2) inhibitors in both T1DM as well as T2DM. Further we have emphasized on use of weight neutral hypoglycaemics to reduce the morbidity with escalation of diabetes. Also we reviewed importance of microRNAs, in HDL transport, significance of use of proprotein convertase subtilisin/kexin type9 (PCSK9) inhibitors. Here we tried to concentrate on reducing same by understanding how this DM might influence the cardiovascular system (CVS) alterations as well as changes caused by them in the amounts of plasma proteins as well as metal ions, changed lipid metabolism (causing changed metabolic control), cardiac lipotoxicity as well as atherosclerosis, endothelial impairment, platelets hyperactivation along with the existence of procoagulant particles in the blood in aetiopathogenesis of CVD with lipid metabolism, sphingosine-1 phosphate; alteration in coagulation parameters in both T1DM as well as T2DM. Thus we conducted a systematic review regarding same with utilization of search engines like PubMed, MEDLINE, Google Scholar, Web of Science, Scopus, Embase, using MeSH terms like fibrinogen; thrombin; antithrombin; antiplasmin; plasminogen activator inhibitor -1 (PAI-1), von Willebrand factor; factor V, factor VII, factor IX, factor X factor, factor XII, tissue factor, metal ions like Ca<sup>2+</sup>ATPase, Zn<sup>2+</sup>, Cu<sup>2+</sup>, Mg<sup>2+</sup>, Fe<sup>3+</sup> iron, platelet hyperactivation; platelet microparticles; complement alteration; endothelial impairment role of lipid metabolism LDL levels, High density lipoproteins High density lipoproteins (HDL) levels in type1 diabetes mellitus as well as type2 diabetes mellitus as well as from 1980's till 2029 till date. We found a total of 650 articles out of which we selected 167 articles for this review. No meta-analysis was done. Thus we consider each step by step in influencing CVS risk and what prophylaxis is needed to avoid the CVD complications in each of DM along with influence in COVID mortality.

**Keywords :** T1DM; T2DM; cardiovascular disease; hypercoagulability in diabetes; platelet hyperactivation; Metal ions alteration; endothelial impairment

## **INTRODUCTION**

In 2017, the combination of diabetes mellitus(DM), that might be type1 diabetes mellitus ( T1DM) as well as type2 diabetes mellitus ( T2DM) were evaluated to be 425 million persons throughout the world [1]. It is anticipated that these figures would escalate to 629 million by 2045[1]. Every kind of DM possesses an aberration in insulin signalling, the peptide hormone that is attributed to stimulate cellular glucose uptake. In the case of T1DM, the insulin liberating  $\beta$ -cells within the islets of pancreas get damaged by the immune system, whereas idiopathically in case of the 2<sup>nd</sup> one[2]. This causes a reduction in insulin generation. T2DM represents a polygenetic disease,with it getting subdivided into 2 subkinds, with or without associated obesity, along with lot of genes making a person prone to form this disease. A heterogenous phenotype is revealed that is secondary to insulin signalling resistance, mostly in view of defective insulin receptors. At the initiation of the disease, insulin liberation is dysfunctional causing hyper insulinemia. Nevertheless, once the disease propagates,  $\beta$ -cells might get destroyed as well as result in hypo insulinemia[3].

Since glucose is implicated in multiple physiological events, a lot of problems accompany both T1DM as well as T2DM. These being lipid metabolism alterations as well as the control of inflammation, vasodilatation, basic cell growth as well as replication. Left unmanaged this hyperglycemia as well as diabetes, can result in deterioration of these physiological alterations potentially resulting in diabetes correlated complications. Specifically, persons having diabetes have a 2-3 times the probability of forming cardiovascular disease (CVD) as compared to those without DM[1]. Like a lot of coagulatory defects are visualized in persons with either T1D or T2DM. Actually a change in the vascular endothelium is observed in both these diabetes types, thus hypertension, premature atherosclerosis as well as vascular diseases that are more extensive might be seen in the afflicted persons in contrast to the general population, hence further escalating their risk of plaque rupture with reference to atherosclerosis as well as thrombus generation[4,5]. Moreover platelets tend to be hyperreactive, in persons having diabetes that result in enhanced activation of prothrombotic

factors as well as reduced fibrinolysis, causing an enhanced risk of thrombosis [4,6]. Additionally, the changes in lipid profile observed in diabetics influences cardiac function as well as can result in lipotoxicity in the heart[5].In view of these factors, as many as 80% of persons with diabetes die secondary to CVD complications[7]. Prognosis, subsequent to a cardiovascular system (CVS) process is poor for persons with diabetes, inspite of exhaustive research on this topic as well as generation of newer treatment [4,8]. Hence it is significant to get insight over the underlying modes which influence haemostatic alterations seen in T1DM as well as T2DM.

Inspite of the enhanced risk of CVD in persons with diabetes, the pathophysiology behind this link is complicated as well as ill understood. However, of the multiple physiological alterations stimulated by diabetes which might influence the CVS are alterations in the amounts of plasma proteins as well as metal ions, changed lipid metabolism(causing changed metabolic control), cardiac lipotoxicity as well as atherosclerosis, endothelial impairment, platelets hyperreactivation along with the existence of procoagulant particles in the blood. This review focuses on the molecular along with cellular alterations that can result in enhanced risk of thrombosis seen in persons presenting with diabetes.

## **METHODS**

Thus we conducted a systematic review regarding same with utilization of search engines like pubmed,MEDLINE ,Google scholar ,Web of Science, scopus, Embase ,using MeSH terms like fibrinogen; thrombin; antithrombin; antiplasmin; plasminogen activator inhibitor -1 (PAI-1),von Willebrand factor ; factor V, factor VII, factor IX, factor X factor, factor XII, tissue factor,metal ions like  $Ca^{2+}$ ATPase,  $Zn^{2+}$ ,  $Cu^{2+}$ ,  $Mg^{2+}$ ,  $Fe^{3+}$  iron,platelet hyperactivation; platelet microparticles ; complement alteration; dendothelial impairment role of lipid metabolism LDL levels, High density lipoproteins High density lipoproteins (HDL) levels in type1 diabetes mellitus as well as type2 diabetes mellitus as well as from 1980's till 2020 till date .

## **RESULTS**

We found a total of 650 articles out of which we selected 167 articles for this review.No meta-analysis was done



escalated in 2 studies [17,38, although decreased in another[19]. Why the variation is queried but might be secondary to a variation in methodology or to the persons studies happening to be at various stages of propagation of the disease in the persons studied. Alterations in plasma protein amounts as well as glucose amounts result in enhanced blood viscosity in case of T2DM[39], as well as an escalating trend has been observed in T1DM, particularly in persons with poor diabetic regulation[40]. Maximum but, not all alteration in protein amounts in case of coagulatory proteins in plasma is , secondary to poor glycaemic regulation as well as thus can get reversed following tight glucose control ,like proteinC, protein S, as well as thrombin amounts have been shown to be enhanced in T2DM following good glycemic control[41]. Certain proteomic alterations get affected by genetic factors. Like the enhancement of fibrinogen amounts as well as factor VII activity in T2DM, are also observed in 1<sup>st</sup> degree relatives of these patients who are nondiabetic[42]. Further chronic inflammation(seen in both T2DM, as well as T1DM) results in complement activation system as well as the kinin-kallikrein system, causing activation of factor XII as well as, escalated amounts of various proteins that include factor VIII, tissue factor prothrombin as well as fibrinogen[6].

The amounts of coagulatory proteins is not the only one influencing coagulation. Whereas enhancement of amounts of PAI-1 are observed in T2DM [[10,17,18,21,34], in case of T1DM it is the activity of the proteins that is reduced[19,44]. Further alterations in fibrin(ogen) function are also more complicated as compared to simply an alterations in amounts, an evaluation of clots generated from fibrinogen purified from persons with T2DM-obtained samples as well as controls detected that the T2DM-obtained samples showed denser as well as less porous clots [45]. The reasoning given is enhanced glycation of fibrinogen in diabetes as well as can be ameliorated with good glycemic control [45]. Besides fibrinogen getting influenced by poor glycemic control, plasminogen, the precursor for plasmin, goes via escalated glycation in persons with T1DM, thus resulting in decreased fibrinolytic activity of plasmin [43]. Moreover the activity of antithrombin is inhibited by methylglyoxal, which is a byproduct of hyperglycemia [46]. Additionally, in healthy persons who had undergone

hyperglycemia as well as hyper insulinemia, the tissue factor pathway has been demonstrated to get activated at an enhanced rate(as compared to and euglycaemia - hyper insulinemia, group)as evidenced by enhanced amount of activated factor VII as well as tissue factor pathway inhibitor ,along with an enhanced factor VII activity[47]. Hence thrombin formation(followed by measurement of amounts of thrombin- antithrombin complex) is enhanced in persons with T2DM or T1DM[48]. Good glycemic regulation is further significant for anti coagulant activity, with enhanced glycemic regulation in T2DM resulting in decrease in thrombin formation[49], as well as enhancement of the anti coagulant activity of antithrombin, protein C as well as proteins S[41].

Hence alterations of both amounts as well as activities of coagulation proteins have significant effects on fibrin clot generation, clot lysis parameters as well as fibrin clot ultrastructure. Enhanced amounts of PAI-1 cause prolongation of lysis time of the fibrin clot in persons presenting with T2DM[10]. The enhanced amount of complement protein C3 observed in T1DM causes the protein getting trapped within fibrin clots at a high rate developed from fibrinogen purified from the blood of persons with T1DM,resulting in delayed fibrin clot lysis[50]. This has also been seen in T2DM cases[51]. In T1DM, both time of lysis as well as C3 amounts enhanced with glycemic regulation that was better [50]. In the same line , $\alpha$ -2 antiplasmin is further trapped within fibrin clots at a high rate in both T1DM, as well as T2DM, that has been demonstrated to enhance resistance to lysis [19,52]. Fibrin clots generated in persons with T1DM,as with T2DM, that has been demonstrated to be more compact as associated with glycemic regulation[53]. Fibrin clots have >resistance to fibrinolysis [10,43,53]. The timing of how long DM has been existing also influences ,with T2DM of over 5 years correlated with enhanced thrombin formation ,decreased fibrinolysis as well as prothrombotic phenotype despite good glycemic regulation[54]. PAI-1 as well as t-PA antigen amounts are also greater in T2DM,that has been present for long time, whereas fibrinogen, plasminogen ,soluble thrombomodulin as well as thrombin –activatable fibrinolysis inhibitor antigen amounts are not influenced[54]. Additionally, variations in the coagulatory proteins amounts as

well as clot parameters were observed in males as well as females with T1DM along with T2DM. Actually fibrinogen as well as PAI-1 amounts are greater in females with T2DM, as compared to males with T2DM, as well as following correction for those factors, females still possess >compact clots, resistant to fibrinolysis as compared to males[55]. Nevertheless, another study with lesser persons observed unaltered fibrinogen, amounts as well as decreased PAI-1 amounts in females with T2DM, that made them more resistant to fibrinolysis [56]. In case of T1DM, clot density as well as fibrinogen amounts in females are akin to that in males, whereas their factor XIII amounts are is greater as compared to males[57]. PAI-1 amounts is also equivalent among females as well as males with T1DM[35]. On evaluating a younger cohort with T1DM (below 30 years old ), females display a prolongation of lysis time as compared to males, but the same is not seen in the elder cohort[57]. Hence in both kinds of DM, these combined alterations cause an enhanced pro-coagulation mode as well as reduction in anti-coagulation as well as fibrinolysis, resulting in an enhanced thrombosis risk.

### Alterations in Metal Ion Homeostasis

Metal ions have multiple parts in blood plasma, that are structural as well as catalytic functions. The plasma, amount of various metal ions is believed to be changed in T1DM as well as T2DM[58]. This has significance as lot of these are essential for the normal action of proteins implicated in coagulation [59,60].  $Ca^{2+}$  is a significant controller of coagulation.  $Ca^{2+}$  is liberated by activated platelets as well as is needed for clotting to occur (especially for tense as well as prothrombinase complexes to work). Chelating agents which bind calcium (like citrate as well as ethylene dimine tetraacetic acid) are usual anticoagulants utilized when collecting blood samples. Lot of studies have observed correlation among high amounts of calcium in the blood as well as the risk of forming T2DM. These studies are the PREDIMED study[61], the Atherosclerosis Risk in Communities (ARIC) study[62], the insulin resistance Atherosclerosis study[63], as well as the Tromso study[64]. Additionally, enhanced amounts of total plasma calcium were also observed in persons with T2DM as compared to healthy controls with no

variation seen among females along with males as well as the time duration of diabetes had no implication on calcium amounts[65]. Serum calcium amounts remain unaltered in T1DM[66]. The influence of enhanced amounts of calcium on coagulation in T2DM have not been totally worked out. In the general population, a meta-analysis has demonstrated that intake of high supplements of calcium >1000mg/day escalates CVS risk in men but not in case of women in whose case intake of calcium has definite benefits over the risks [67]. In this particular study calcium administration was observed to enhance the risk of coronary artery calcification and atherosclerosis in both sexes [67]. Nevertheless, not all calcium that was delivered as supplements will get absorbed as well as most of the absorbed extra calcium would be stored in bones. In subjects with T2DM, plasma calcium amounts are enhanced. Hence more studies are essential to find out the role of hyper coagulability observed in subjects with T2DM might get reasoned out by changes in plasma calcium amounts.

Additionally, besides  $Ca^{2+}$ ,  $Zn^{2+}$  is also significant in controlling coagulation[59]. Just like  $Ca^{2+}$ ,  $Zn^{2+}$  also gets liberated by activated platelets, along with injured epithelial cells as well as atherosclerotic plaques. Even neutrophils, erythrocytes, lymphocytes, also possess them thus might be liberated at areas of damage (though this needs to be verified ([68]).  $Zn^{2+}$  is further implicated in all steps of coagulation like procoagulatory, anticoagulatory, profibrinolysis as well as anti fibrinolysis modes along with platelet activation as well as aggregation[59]. Deficiency of zinc results in bleeding as well as platelet aggregation impairments[59]. Both in T1DM as well as T2DM, zinc amounts are decreased as compared to healthy individuals[69]. Nevertheless, in free fatty acids,  $Zn^{2+}$  ions get transported via serum albumin, that is further the major transporter of free fatty acids (FFAs) [70]. If pathological amounts of FFAs binds to the high affinity binding sites FA2 on serum albumin, the protein conformation alterations as well as the major  $Zn^{2+}$  binding site gets impaired as well as no longer has the ability of  $Zn^{2+}$  binding [70]. If pathological amounts of FFAs exist in the blood, like in the case of T2DM, as well as in certain T1DM individuals, the handling /buffering of  $Zn^{2+}$  by serum albumin gets impaired as well as plasma zinc speciation (the molecules with which it gets bound ) gets changed

[71]. Utilizing size –exclusion chromatography –ICP-MS,  $Zn^{2+}$  gets redistributed among rest of plasma proteins in the pathophysiological amounts of FFAs existing in blood [72]. With the knowledge that lots of coagulatory proteins get controlled by  $Zn^{2+}$ , this changed  $Zn^{2+}$  speciation can cause impairment of coagulation, causing an enhanced platelets accumulation, enhanced fibrin clot density as well as delay in fibrinolysis, hence potentially being a part of the enhanced risk of thrombosis observed in T2DM.

$Mg^{2+}$  is also significant as far as coagulation is concerned.  $Mg^{2+}$  has the capacity of potentiating the factor X activation via activated factor IX, whereas in the existence of activated factor VIII, phospholipids as well as  $Ca^{2+}$ , [73], the activation of factor IX, by activated factor VII –tissue factor complex [73], as well as the in activation of factor V by activated protein C [74]. Further  $Mg^{2+}$  influences clot time by, escalation of clotting at low amounts as well as slowing or totally avoiding fibrin clotting at high amounts (in view of it competing with  $Ca^{2+}$ , for binding to coagulation factors [75]. Moreover  $Mg^{2+}$  reduces fibrin clot lysis time, probably via inhibition of PAI-1 in the existence of thrombin as well as vitronectin [76]. Magnesium deficiency in both humans as well as animals results in enhancement of coagulability [76]. Magnesium deficiency has been seen in both males as well as females in T1DM, despite the action being more prominent in females [58]. In T1DM, Magnesium deficiency correlated with late fibrinolysis as well as >thrombotic risk [39]. Subjects with T2DM, also have a higher risk of Magnesium deficiency as well as might be influenced by modes akin to that in T1DM [77]. Poor glycaemic regulation correlates with Magnesium deficiency in view of decrease of tubular reabsorption of Magnesium [58].

Plasma copper total amounts are enhanced in T1DM as well as T2DM [78]. The probable action of copper on coagulation is clear, in spite of  $Ca^{2+}$  as well as  $Cu^{2+}$  representing essential co factors of various coagulation proteins (like coagulation factors V as well as VIII) [79]. Escalated dietary amounts of copper in rats (that got depicted by amounts of copper in the liver) were observed not to influence clot time when clotting was stimulated by thromboplastin as well as  $Ca^{2+}$  (on trying to assay factor X, thrombin as well as fibrinogen activation) or  $Ca^{2+}$  as well as

phospholipids (on evaluating the full extrinsic pathway of coagulation) [80]. Nevertheless, greater than 95% of copper gets carried by the protein ceruloplasmin [51]. Amounts of ceruloplasmin are escalated in subjects T1DM, probably secondary to inflammatory events [76]. In T2DM, amounts of ceruloplasmin might be decreased or escalated, with a meta-analysis has demonstrated that globally amounts of ceruloplasmin are escalated although not significantly ( $O=0.6$ ), with sex not influencing any of the parameters [69]. T1DM subjects have deficiency of iron, how long diabetes has been present or sex is immaterial with regards to deficiency of iron. Nevertheless, menstrual cycle mattered [82]. For the ones who are deficient in iron, diet administration of  $Fe^{3+}$  salt remains the treatment of choice [83]. This supposedly influences coagulation by prolongation of clotting time of plasma (probably by competition with calcium in binding with the clotting factors), fibrin clot getting weaker (via crosstalk with fibrinogen as well as fibrin), along with stimulation of precipitating the plasma proteins to generate “insoluble coagulums” that have resistance to get lysed, (significantly by binding as well as breakdown of serum albumin as well as probably transferrin), hence escalating the chances of thromboses [83]. Additionally,  $Fe^{3+}$  has been demonstrated to start the fibrinogen transformation into fibrin-like polymer, parafibrin, which has resistance to proteolysis as well as this gets deposited in the blood vessels [84]. Hence, the changed amounts of plasma metal ions in T1DM as well as T2DM subjects would influence coagulation as well as the chances of generation of cardiovascular diseases (CVD’s).

### Alterations in Lipid Metabolism at the initiation of Atherosclerosis as well as lipotoxicity

Alterations in Lipid Metabolism occurs both in T1DM as well as T2DM. Plasma cholesterol, low density lipoprotein (LDL), as well as triglyceride amounts are escalated, whereas high density lipoproteins (HDL) amounts are reduced in T2DM subjects, along with subjects with T1DM as well as poor glycaemic regulation [85]. No alterations in cholesterol amounts in subjects with T1DM as well as good glycaemic regulation might be deceiving as both profiles of lipids along with their functioning is changed [[86]. Usually high total cholesterol, as well as LDL amounts have

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been considered as a main factor for atherosclerosis as well as CVD's generation in the general population. Nevertheless, Ravnskov et al., debated in a recently conducted review of literature that high total cholesterol, as well as LDL amounts can't be implicated as causative factors for these diseases[87]. The alteration in these views is reasoned out as the failure of maximum meta-analysis to accurately account for the negative studies[87]. Further they also said that the correlation among CVD's as well as LDL or cholesterol amounts observed in some cohorts can be reasoned out by various modes. A probable reason is that infections can result in CVD's as well as LDL can take part in immune working by adhering to along with causing inactivation of microorganisms as well as their toxic products[87]. Further stress is also responsible for CVD's as well as escalated generation of adrenaline as well as nor adrenaline aid in hypertension as well as hyper coagulation, along with cholesterol being a precursor for cortisol as well as rest of the stress steroid hormones [87]. Nevertheless, if this opinion points to what actually occurs at the molecular setting is not obvious since this study only looked at the general population and not in T1DM as well as T2DM subjects, where lipid decreasing drugs are an essential part of therapy for avoiding any generation of complications that are CVD's [85,86].

In case of diabetes, high LDL amounts are correlated with CVD's, nevertheless they do not anticipate the risk of CVS in case of T1DM[86,88]. However, greater amounts of "small dense LDL" exist both in T1DM as well as T2DM as well as these types of LDL penetrate with greater ease in the arterial wall as compared to "large buoyant LDL"[89,90]. Further 'small dense LDL' have a greater proneness towards oxidative stress, possess a decreased affinity towards LDL receptors as well as possess escalated half life in plasma as compared to "large buoyant LDL"[89,90]. Additionally, they get glycosylated with greater ease as well as carry a greater percentage of apolipoprotein B, that gets exposed to glucose[91]. Moreover oxidized LDL inhibits endothelial nitric oxide(NO) generation[92] can also be picked up by macrophages as part of the atherosclerotic plaque generation[90]. These properties are, correlated with endothelial impairment as well as CVD's[86,90].

For long HDL has been believed to possess protective characteristics against CVD's. Nevertheless, recent proof has demonstrated that low HDL amounts is correlated with an enhanced CVD's risk, however high HDL amounts does not possess a protective action as well as might even be dangerous, as has been demonstrated in general population as well as in T1DM subjects[93]. These unanticipated outcomes might be reasoned by the presence of various HDL subspecies having various functions[94]. Thus it might be of advantage to directly evaluate HDL functions, like its part in facilitating reverse cholesterol transport (i.e. the motion of cholesterol from peripheral tissues towards the liver to get excreted via bile)[94]. Like when macrophages exist in the arterial walls collect in the form of extra cholesterol, the ATP binding cassette transporters A1 as well as G1 are stimulated and this ends in the efflux of cholesterol, from macrophages towards the HDL[94]. This efflux of HDL is more advantageous anticipator of CVD as compared to HDL amounts[95], despite some rest of studies have not agreed on this[96]. There is a reduction of efflux of HDL in T2DM subjects[97] or T1DM[98]. This might be secondary to reactive oxygen species(ROS), that are enhanced in diabetes subjects, might influence HDL function[99]. Other than its part in cholesterol efflux, HDL further possesses anti atherosclerotic action, since it facilitates NO generation in the endothelial cells, a necessary part of endothelial function[94]. Further HDL possesses an anti inflammatory along with antioxidant actions[94]. A study that compared the actions of HDL taken from subjects with T2DM as well as controls demonstrated that in T2DM, HDL could not stimulate nitric oxide (NO) generation in the endothelial cells, as well as did not facilitate endothelial healing[100]. Additionally, in T2DM, HDL possess decreased amount of HDL –correlated sphingosine-1 phosphate(SIP), that causes a decreased capacity to activate endothelial nitric oxide synthase( NOS)[101]. Moreover in subjects with T1DM possesses same extent of SIP as well as apolipoprotein M in complete HDL as controls. Nevertheless, the HDL –correlated apolipoprotein M / SIP complex shift to a separate subset of HDL, from buoyant HDL to dense HDL, where it possesses decreased anti inflammatory actions secondary to changed SIP<sub>1</sub> receptor activation[102].

Commonly hypertriglyceridaemia is correlated with T1DM as well as T2DM[103]. The cholesterol ester transfer protein(CETP) aids in exchange of cholesterol as well as triglycerides among very density lipoprotein( VLDL) as well as HDL[104]. Once the plasma amounts of triglycerides is very enhanced, there is a disturbance of the equilibrium, HDL gets deprived of cholesterol as well as rich in triglycerides[104]. This causes a dysfunctional HDL structure, since the hydrophobic core of the triglycerides partly projects to the HDL surface[105], along with interfered HDL function[106] as well as ultimately endothelial dysfunction. Opposite to HDL – cholesterol amounts, HDL – triglycerides have been demonstrated to be a good marker of escalated CVS risk in the general population[107], along with in T2DM subjects or those with metabolic syndrome(MetS) [104].

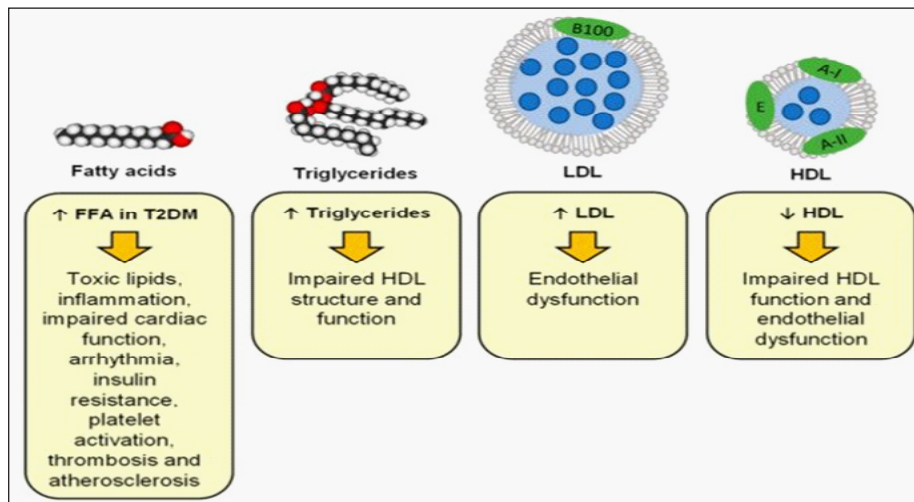
Further an, alteration of FFA, as well as the plasma amounts of FFA, along with that of the main species of FFA, are enhanced in T2DM subjects[71], whereas they are decreased in T1DM subjects as well as those with poor glycaemic regulation[108]. Significantly, FFA are controllers of a lot of physiological events along with their impairment might result in Significant consequences[5]. The commonest one is the adherence of extra FFA on the endothelial walls of blood vessels as well as their consequent collection that causes the generation of Atherosclerotic plaques[5]. These plaques can result in blood vessels that become narrower, hence promoting their total blockade, as well as rupture of plaques in a prothrombotic process which can instigate thrombosis as well as embolism[109]. Additionally, the FFA translocate CD36 that is present on macrophages as well as platelets, along with activated by FFA to trigger coagulation[110]. Moreover, escalated plasma FFA amounts directly influence fibrin clot parameters; the saturated FFA, stearic acid, has been demonstrated to escalate the diameter of fibrin fibres in a purified system, whereas an unsaturated FFA oleic acid decreased it [111]. Stearic as well as oleic acids also escalated clotting time as well as decreased the mechanical stability of the clot via reduced rigidity, a greater deformability as well as reduced resistance to shear stress [111]. Additionally, plasma amounts of FFA further influence the cardiac function since they escalate proneness to oxidative stress as well

as ischaemic injury [112]. Actually, escalated FFAs also result in toxic lipids (specifically, diacylglycerides as well as ceramides) hence facilitating endoplasmic reticulum (ER) stress, mitochondrial function impairment as well as development of reactive oxygen species(ROS) [5]. This results in inflammation, insulin resistance (IR) as well as apoptosis of cells [5]. Further these toxic lipids stimulate protein kinase C( PKC) as well[5]. This PKC activation interferes with the intracellular  $Ca^{2+}$  handling by the cardiac area, interfering with cardiac contractility as well as facilitating its fibrosis along with hypertrophy[112]. Whereas n-3unsaturated FFAs have been demonstrated to possess antiarrhythmic as well as cardioprotective actions, saturated FFAs can result in electro physiological remodelling as well as prolonged as well as fatal arrhythmias [113]. Hence the alterations of lipid amounts as well as lipid metabolism observed in T1DM as well as T2DM might have a robust influence in generation of CVD as shown in **figure2**.

### Endothelial Function Impairment

By definition this represents the reduced generation as well as /or presence of NO, a molecule that is implicated in vascular homeostasis, vasodilation along with platelet inhibition as well as the upsetting of balance among vasodilators as well as vasoconstrictors within the vasculature. This Endothelial function impairment occurs prior to the generation of atherosclerosis as well as escalated chances of generation of CVD. diabetes is correlated with a series of alterations of endothelial function, secondary to various factors like an escalated chronic inflammation as well as oxidative stress in both T1DM as well as T2DM[148]. Escalated plasma amounts of FFA results in impairment of  $Ca^{2+}$  as well as insulin signalling, causing a decrease in generation of NO, hence causing escalated endothelial permeability [109]. Activation of the NLRP3 inflammasome by escalated FFA further escalated this permeability [109]. Besides that escalated FFA influence the renin-angiotensin system, causing impairment of arterial blood pressure [109]. Additionally, the activation of the nuclear factor kappa B(NFκB) inflammation pathway (by saturated FFA, but not the poly unsaturated FFAs) results in an escalated generation of superoxide in the endothelium [109], that itself escalated the amounts of a wide range of enzymes that are the oxidative enzymes





**Figure 2.** Courtesy reference no-9 An altered lipid profile increases the risk of cardiovascular disease in T1DM and T2DM. Abbreviations used: FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T2DM, type-2 diabetes mellitus.

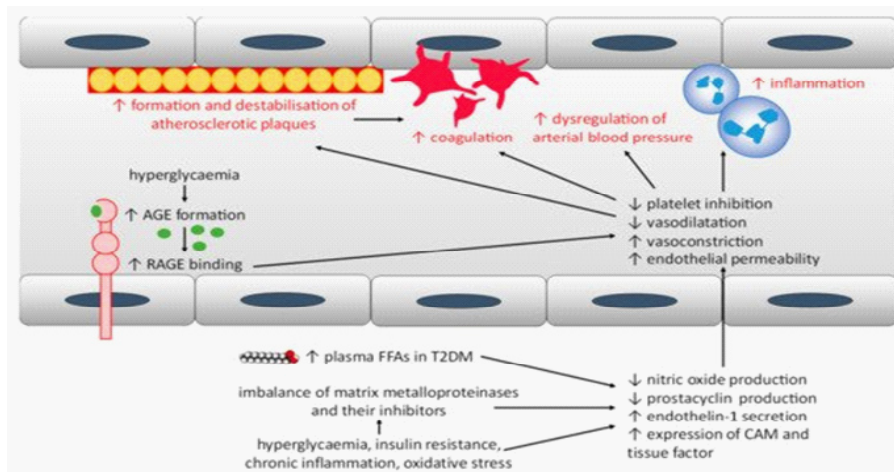
systems like NADPH oxidase, xanthine oxidase, cyclooxygenases, lipoxygenases, myeloperoxidases, cytochrome P 450 monooxygenases, uncoupled nitric oxide synthase(NOS) as well as peroxidases. Together these enzymes inactivate NO. Moreover, combined oxidative stress as well as hyperglycemia observed in diabetes results in the glycation of plasma proteins as well as lipids along with develop AGES[114]. These AGEs subsequently collect in the vessel walls as well as interfere with cell function, significantly by binding to AGEs receptors(RAGEs) [114]. Signalling via RAGEs downregulates NOS in endothelial cells as well as upregulates the expression of vascular cell adhesion molecule (VCAM), intracellular adhesion molecule(ICAM), E-selectin(3cellular adhesion molecules) monocytes chemoattractant proteins(a controller of migration as well as infiltration of monocytes as well as macrophages), endothelin 1(a vasoconstrictor) as well as tissue factor[114]. IR by itself further decreases NO generation as well as stimulation of endothelin 1 liberation [115]. Impairment of these pathways aids in pro inflammatory as well as prothrombotic characteristics of the endothelium in diabetes. Additionally, diabetes is correlated with reduced endothelial generation of prostacyclin, that is a vasodilator as well as inhibits activation of platelets[114]. Moreover, Matrix metalloproteinases(MMP), represent Zn<sup>2+</sup> binding proteases which breakdown parts of extracellular Matrix (ECM), along with whose generation is upregulated significantly by, hyperglycemia pro

inflammatory mediators as well as ROS[116]. MMP's amounts, are correlated with generation of CVD as well as all cause mortality in T1DM[117,118], as well as with CV organ injury in T2DM[119]. In diabetes, they escalated inflammation, endothelial function impairment, vascular remodelling as well as thrombus generation[120]. The loss of balance among MMPs along with their inhibitors demonstrated in diabetes is correlated with the generation along with instability of atherosclerotic plaques[121]. Hence, endothelial function impairment is a main aetiological factor in aiding in chances of CVD in T1DM as well as T2DM subjects as demonstrated in **figure 3**.

### Hyper activation of Platelets

A lot of the crucial influencing the coagulation system in diabetes, implicates Platelets. During normal physiological process Platelets get activated secondary to external stimuli that are thrombin(that binds to G protein coupled receptor( GPCR), PAR1, PAR3, PAR4), collagen(that binds to the receptor GPVI- $\alpha$ IIb $\beta$ 1) as well as thromboxane A<sub>2</sub>. The P2Y<sub>12</sub> pathway can amplify these stimuli by stimulating the liberation of thromboxane A<sub>2</sub> as well as ADP from the internal stores. Via intracellular Ca<sup>2+</sup> flux, activation occurs, resulting in alteration in the amounts of expression of surface glyco proteins(like integrins) that can then work as receptors for Platelet agonists as well as for adhesion proteins implicated in platelet aggregation. Following platelet aggregation, P-selectin

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**Figure 3.** Courtesy reference no-9 The changes in inflammation, oxidative stress and blood levels of glucose, insulin and lipids associated with T1DM and T2DM cause endothelial dysfunction, which itself results in an increase in the risk of cardiovascular disease. Abbreviations used: AGE, advanced glycation end-products; CAM, cell adhesion molecules; FFA, free fatty acid; T2DM, type-2 diabetes mellitus; RAGE, advanced glycation end-product receptors, T1DM, type-1 diabetes mellitus; T2DM, type-2 diabetes mellitus.

translocates from  $\alpha$ -granules membranes to the plasma membranes, as well as the GPIIb-IIIa complex on plasma membranes goes via a conformational alteration, which exposes a fibrinogen binding area. Platelets then liberate the granular contents like  $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$  coagulation factors, growth factors, stick to the sub endothelial surface ( GPIb-V binds to vWF, GPIIb-IIIa or fibrinogen, as well as fibrin along with rest of coagulation factors crossreact with the platelets surface), as well as collect to generate a thrombus. Control of platelet function takes place via the work of antiaggregating prostacyclins as well as NO, both that get liberated by intact endothelial cells. Insulin inhibits the platelets responses towards stimuli via the  $\text{P2Y}_{12}$  pathway as well as sensitize platelet toward the antiaggregating action of prostacyclins as well as NO.

The hyperglycemia observed in T1DM as well as T2DM causes i) decreased prostacyclins as well as NO generation from the endothelium as well as NO generation from the platelets resulting in a disrupted balance of the antiaggregating mode [122]; ii) decreased insulin sensitivity of platelets in T2DM (or decreased insulin amounts in T1DM), that results in decreased inhibition of  $\text{P2Y}_{12}$  pathway, that itself causes a decreased platelets threshold to stimuli as well as hence enhanced platelet reactivity [123]; iii) glycation of proteins at the surface of platelets, that results in changed activity, in addition to signalling

by receptor proteins as well as to decreased platelet membrane fluidity, hence escalating platelet sensitivity to thrombin as well as platelet stickiness [6, 122, 124] iv) escalated activation of PKC that escalates platelet activation [125] v) enhanced oxidative stress, that activates the PKC pathway, however also results in an enhanced intracellular  $\text{Ca}^{2+}$  signalling for escalating platelet activation as well as aggregation [125]; vi) reduced generation of antioxidants like glutathione, that has been correlated with enhanced generation of thromboxane  $\text{A}_2$ , that results in escalated platelet activation [122, 126]; vii) enhanced basal  $\text{Ca}^{2+}$  amounts in platelets along with impairment of  $\text{Ca}^{2+}$  homeostasis that directly controls platelet activation, platelet morphology, in addition to starting of coagulation [122, 126] viii) enhanced surface expression of glycoproteins like GPIb as well as GPIIb-IIIa along with enhanced activation of GPIIb-IIIa, resulting in enhanced binding of vWF as well as fibrin(ogen), both leading to enhanced platelet aggregation [122, 127].

Moreover the hyper activation of Platelets in subjects with diabetes points that they get used at a fast pace with a rapid Platelet turnover [122]. This results in the formation of new platelets which are inherently hyperactivate by themselves [128]. Additionally, in both T1DM as well as T2DM platelet counts have been seen to be greater [169]. This change has a positive influence following good glycaemic regulation

only in T1DM subjects, whereas subjects with T2DM, possess a greater number of large platelets, that show enhanced hyperreactivity[122,129,]. Hence in subjects with diabetes, platelets have higher activity, that results in escalated stickiness, activation as well as hyper activation aggregation along with generation of Platelet-obtained microparticles [122]. Together, these alterations cause an enhanced initiation of thrombus generation as well as escalated liberation of procoagulatory molecules by platelets like  $Ca^{2+}$ ,  $Zn^{2+}$ , fibrinogen, vasoconstrictors as well as oxidative reactive species that escalated coagulation along with atherosclerotic event in both T1DM as well as T2DM (figure4)[122].

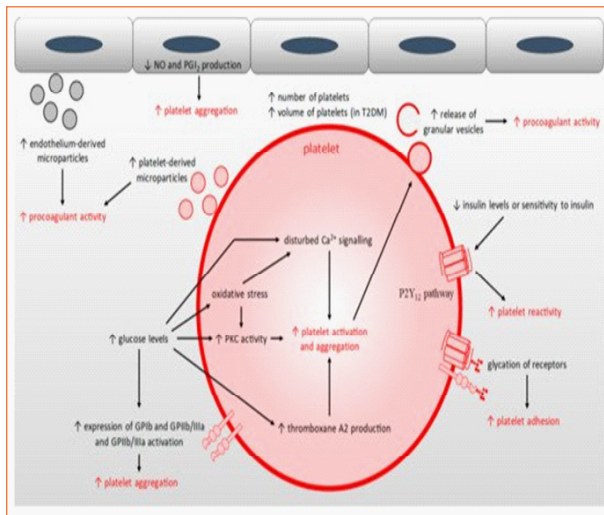
### Microparticles that are Procoagulatory

During cell growth, proliferation, activation as well as apoptosis cells crosstalk via liberation of ECV. Microparticles, represent a heterogenous kind of vesicles possessing a diameter of 0-0.1  $\mu m$  as well as total cargoes that include lipids, proteins as well as microRNAs based on their place of arising[170]. The liberation of microparticles by cells gets stimulated significantly via pro inflammatory cytokines, advanced glycation endproducts (AGEs), oxidative stress, LDL, as well as hyperglycemia along with their size, structure as well as cargo vary based on the cell kind along with the stimuli initiating their generation [122]. Regularly microparticles exist in the blood, Nevertheless, a lot of CVD are correlated with enhanced amounts of these microparticles, particularly those obtained from platelets as well as endothelial cells[131]. In case of T2DM amounts of these microparticles in the blood are enhanced; Specifically, endothelial-obtained microparticles that have abundant CD31, CD62E, CD105 as well as CD106[132], along with platelet-obtained microparticles possessing abundant fibrinogen, (2 times as escalated compared to non diabetic subjects[133], as well as with -selectin[134]. Additionally, a proteomic evaluation conducted on microparticles obtained from subjects with T2DM as well as controls demonstrated that in T2DM, proteins implicated in Platelet activation, cell stickiness, as well as inflammation get differentially expressed [135]. Great amounts of platelet-obtained microparticles get correlated with atherosclerotic propagation as well as arterial thrombosis in subjects with T2DM[130]. Microparticles amounts in T2DM are an independent

anticipator of harmful CVS processes (adjusting for age, gender, hyperlipidemia, smoking as well as statin utilization)[130]. Subjects with T1DM also possess escalated amounts of endothelial as well as platelet-obtained microparticles that have enrichment with annexin V[136,137]. Further in T1DM, escalated procoagulant activity was observed to correlated with the complete amounts of microparticles that have enrichment with annexin V[137]. The amounts of endothelial- as well as platelet- obtained microparticles along with procoagulant activity had a direct association with Hb A1c amounts in subjects with T1DM[136,137].

Microparticles generated from platelets are severely prothrombotic along with promote thrombin formation[131]. These particular microparticles get enriched along with tissue factor, that makes a blood-borne reservoir of this particular protein[131]. Whereas tissue factor gets exposed to the blood vessel at the time of coagulation stimulates thrombus generation, the blood-borne tissue factor is implicated in the progression of coagulation[131]. Hence the escalation of blood-borne tissue factor in T2DM aids in the prothrombotic phenotype of this disease[130]. These platelet-obtained microparticles can get trapped within the generating thrombus crosstalks of CD15, CD18 as well as, tissue factor with the thrombus [130]. Moreover, smooth muscle cells--obtained markedly prothrombotic that have been enriched in tissue factor can get struck in atherosclerotic plaques along with liberated on plaques erosion or rupture[138]. Microparticles can generate a binding surface for more platelets getting recruited as well as for fibrin following plaques getting disturbed[130]. Microparticles obtained from activated platelets can further activate rest of platelets by liberation of arachidonic acid[130]. Additionally, besides tissue factor, microparticles can promote thrombin formation in a factor XII-based way (for erythrocytes- as well as platelets obtained microparticles) along with a factor XI-based way (for erythrocytes-obtained microparticles)[138,140]. Hence the escalation of procoagulatory existing in subjects with T1DM as well as T2DM take part in markedly thrombotic chances correlated with these diseases (figure4).

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**Figure 4.** Courtesy reference no-9 Mechanisms resulting in the hyper-reactivity, hyper-activation, aggregation and adhesion of platelets in T1DM and T2DM. Abbreviations used: NO, nitric oxide; PGI<sub>2</sub>, prostacyclin; PKC, protein kinase C; T2DM, type-2 diabetes mellitus.

### Thrombotic Risks Alteration Among type1and type2 diabetes mellitus

In spite of the various causative factors of these diseases, there are a lot of commonality among the excessive coagulability state observed in subjects with T1DM as well as T2DM, along with variations. Both of them have the properties of hyperglycemia, changed insulin metabolism, dyslipidaemia, changed endothelial impairment, oxidative stress as well as inflammation. Nevertheless, subjects with T2DM, possess escalated FFA amounts that are not observed in T1DM, along with have the ability to influence the control of a lot of physiological events, like changes in fibrin clot parameters, endothelial impairment, Atherosclerotic plaque generation along with cardiac lipotoxicity. Additionally, insulin amounts are usually enhanced in T2DM as well as associated with IR, whereas they are suppressed in T1DM (although IR can show up in T1DM[141]).  $\beta$ -cells might be injured in T2DM, resulting in decreased insulin generation along with enhanced platelet reactivity[3]. Moreover both disease are correlated with differentially changed plasma amounts of metal ions, resulting in impairment of coagulation through various modes. Lastly, PAI-1 amounts are escalated in T2DM, although decreased in T1DM, despite both the disease kinds have a correlation with prolonged

fibrinolytic lysis times. These differences have a great significance as well as need to be considered when doing treatment of this disease.

Occasional studies have evaluated if subkinds of T1DM as well as T2DM possess an impact on these prothrombotic factors. Obese subjects with T2DM can be anticipated to possess escalated free fatty acids amounts as compared to nonobese subjects with T2DM, with prothrombotic action of escalated FFAs already detailed. Additionally, Obese subjects with T2DM possess higher risk of thrombosis as compared to nonobese subjects with T2DM since they demonstrate delayed fibrinolysis, greater plasma amounts of vWF as well as fibrinogen, along with greater amounts of factor VII as well as factor VIII activity [142]. T2DM subjects who also possess a higher Genetic predisposition to type 2 Diabetes have a chance of correlation with extra prothrombotic factors as compared to T2DM subjects with no Genetic predisposition, actually subjects with some Genetic predisposition to T2DM but still not generated T2DM have an enhanced risk of cardiovascular disease generation [143,144]. Those genes that are "at risk" are genes implicated in lipid oxidation (like paraoxonase), anti oxidation (SOD) as well as ANTI-inflammation (adiponectin [145]). On comparison of non fulminant type 1 Diabetes with fulminant type 1 Diabetes (i.e a subkind of idiopathic T1DM which by definition is a small time period among symptoms initiation as well as onset, occurring from the fast as well as total breakdown of  $\beta$  cells from pancreas) over 5 years, with 1 study observing no variation in the generation of Diabetic microangiopathy complication [146], as compared to another one that observed a greater subjects number with generation of microangiopathy incidence in the fulminant T1DM group as compared to autoimmune one [147]. Idiopathic T1DM subjects were further seen to possess greater body mass index (BMI) as well as LDL amounts, a greater visceral adiposity index (which is a pointer of low grade inflammation as well as cardiovascular risk), greater Obese amounts (thus presumably a >amount of plasma FFA along with impairments they cause) as well as hypercholesterolemia along with lower HDL amounts as compared to subjects with autoimmune T1DM [148]. The amounts of micro as well as macrovascular complications were same in both groups [148]. Hence greater studies

are required to get insight how various kinds of T1DM as well as T2DM vary with regards to cardiovascular biomarkers as well as thromboses risk.

### **PRESENT THERAPIES,CONCLUSIONS AS WELL AS FUTURE DIRECTIONS**

In view of variations in influence of T1DM as well as T2DM on coagulation pathways , subjects with these diseases have separate responses for various agents meant for decreasing thromboses risk ,hence Specific care is required for deciding the treatment regimen for a subject ,as earlier detailed by Alzahrani SH as well as Ajjan RA[4] regarding actions of antiPlatelet drugs,drugs which reduce lipids along with hypoglycaemic agents on coagulation system of subjects with DM. Present therapies forDiabetes concentrate on lifestyle alterations for controlling glycaemia[149]. Hyperglycemia initiate a lot of coagulation alterations as well as good regulation of glycaemia has been demonstrated to markedly decrease a lot of symptoms,that are normalizing the plasma amounts of a impairment as well as plasma amount of microparticles. If lifestyle alterations are not enough ,drugs can be used ,Many drugs aid in good regulation of blood glucose amounts like metformin or glipizide(a sulphonylurea class of oral hypoglycaemic agent )that has been demonstrated to decrease plasma PAI1in case of monotherapy as well as much greater chances on use as combination[150]. On reducing blood glucose amounts decreases the risk of generation of cardiovascular disease in case of diabetes but just to a particular amount, since even hypoglycaemia has shown to be prothrombotic as well [51]. By itself metformin has been advantageous in terms of attaining weight reduction (as well as hence possibly a decrease in plasma FFA amounts), bettering of haemostatic function(with more efficacious fibrinolysis as well as decreased clot generation proneness )suppression of inflammation along with oxidative stress, enhancing endothelial function,besides decreasing atherosclerosis plaques generation.This also means inhibiting monocytes to macrophage getting converted ,decrease in invasion of arterial wall by the inflammatory as well as decreased lipid uptake by these activation of macrophages, present within these Atherosclerotic plaques[151]. It is not sure if metformin decreases cardiovascular risk. On utilization of metformin by

itself as demonstrated by 2 meta-analysis, it does not possess enough action on cardiovascular disease in case of T2DM, nevertheless, these evaluations included shortterm studies in general[152], whereas another study where patients had a long term follow up (as per the UKProspective Study )have demonstrated it to be advantageous[151,153]. Other types of oral hypoglycaemics like dipeptidyl peptidase-4 inhibitors i(DPP-IV) as well as sulphonylureas did not cardiovascular benefits in T2DM[154]. DPP-IV inhibitors were documented to inhibit Platelet aggregation by interference with tyrosine phosphorylation of Platelet plasma membrane  $Ca^{2+}$ ATPase channel, hence restricting the collection of intracellular  $Ca^{2+}$ [155]. Further they enhanced endothelial NO signalling in the vascular system,thus decreasing endothelial dysfunction as well as decreasing inflammation as well as Atherosclerosis plaques generation along with oxidative stress [156,157]. Thiazolidinediones, i.e another class of oral hypoglycaemics , possesses advantageous actions on cardiovascular disease risk but further exaggerates the risk of congestive heart failure(CHF)[154].2 new classes of glucose lowering agents like the sodium-glucose –cotransporter 2(SGLT2)inhibitors as well as Glucagon –like Peptide -1(GLP1) GLP1 receptor agonists [reviewed by earlier ]have been documented to have advantageous actions in CVD risk in T2 DM as well as established CVD[154,reviewed by us in 158,159]. Further we have reviewed on how atherosclerosis is initiated in both T1 DM as well as T2 DM[160]. GLP1 receptor agonists inhibit Platelet aggregation GLP1 as well as thrombus generation via escalated NO generation by activated endothelial NOS, thus suppressing endothelial dysfunction[161]. Further they reduce postprandial dyslipidaemia [161]. SGLT2 inhibitors,are usually efficacious in reducing CHF since they escalate cardiac cell metabolism, decrease cardiac fibrosis ,inhibit  $Na^+/H^+$ exchange in myocardial cells, manipulate adipokine as well as cytokine generation, enhance ventricular loading situations as well as reduce blood pressure(BP)[162].

Lipid reducing agents like statins are further of use basically for reducing total cholesterol as well as LDL amounts.Besides their actions on LDL. these Lipid reducing agents have more advantages in T2DM. Actually a lot of these agents like statins as well as

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fenofibrate, further influence FFA as reviewed in ref 5. This is a significant action since FFAs control a lot of physiological events, that are endothelial function. Moreover Lipid reducing with statins can restrict the amount of circulating microparticles by decrease of thrombus generation as well as the expression of tissue factor, P-selectin, and GPIIIa on Platelets obtained microparticles in patients with peripheral arterial occlusive disease[170,163]. They further enhance the amounts as well as anticoagulant action of protein C as well as proteins along with antithrombin, decrease the amount of procoagulatory prothrombin, factor V, factorVII, factorVIII, factor IX as well as factor X, decrease the amount of antifibrinolytic PAI1, as well as decrease the expression of tissue factor BY endothelial cells [4,164]. Nevertheless, statins have been documented to escalate[41] as well as reduce [165] the amounts of antithrombin. statins have been demonstrated to decrease endogenous thrombin potential as well as thrombosis risk in T2DM along with atherosclerotic risk via suppression of inflammation along with endothelial dysfunction[4].If statins are consumed in combination with rest of Lipid reducing drugs like ezetimibe or proprotein convertase subtilisin/kexin type9(PCSK9) inhibitors demonstrate advantageous actions on cardiovascular disease risk [166]. Additionally, drugs meant for enhancement of HDL-Cholesterol amounts like niacin, fenofibrate as well as CETP inhibitors have been fashioned. It is of significance to emphasize that these drugs do not reduce any further cardiovascular disease risk when delivered to subjects who are already consuming statins[137]. However, fenofibrates further have certain actions on the coagulation system, that are reduced fibrinogen, tissue factor, factorVII as well as PAI1[4].

In case treatments that are targeting both glycaemia as well as lipid amounts are not enough for decreasing cardiovascular risk Markers in diabetes, antiplatelet agents can also be given[4,5,163-165]. That subjects with DM display lower response to antiplatelet agents is well understood, but still double therapy with aspirin as well as P2Y<sub>12</sub> inhibitors clopidogrel is advised even now[9]. Other methods are getting evaluated for decreasing thrombosis risk in subjects with T2 DM, like directly targeting the hypofibrinolysis observed in DM, like reviewed via Keaney et al[63]. These new agents inhibit thrombin

activatable fibrinolysis inhibitor as well as PAI1 along with reduce the incorporation of  $\alpha$ -2 -antiplasmin as well as C3 proteins into fibrin clots .

Thus from this review it is obvious that diabetes represents a complicated disease which robustly influences the haemostasis as well as the risk of cardiovascular disease generation by multiple modes. These being changes in amounts of plasma proteins as well as metal ions, changed lipid metabolism (causing changed metabolic control), cardiac lipotoxicity as well as atherosclerosis, endothelial impairment, platelets hyperreactivation along with the existence of procoagulant particles in the blood. Hence it is of significance to have insight regarding how these modes vary in T1 DM as well as T2 DM for proper therapy of these diseases along with decreasing thrombotic risks in subjects afflicted with these diseases.

Further Chen et al. in a retrospective study in enrolled inpatients with COVID-19 from Wuhan China evaluated the risk factors for the death in patients with COVID-19 with type 2 diabetes mellitus (T2DM) which comprised of 1105 patients and concluded that Coagulopathy was a major extrapulmonary risk factor for death in inpatients with COVID-19 with T2DM rather than acute cardiac injury (ACI) and acute kidney injury (AKI), which were well associated with mortality in inpatients with COVID-19 without T2DM[166].

Further in view of the impact of vitamin K in abrogating diabetes-correlated complications, specially those linked with platelet activation and coagulation is not understood . Mokgalabani et al are planning to conduct A systematic review of studies published on the MEDLINE (PubMed), EMBASE, and Google Scholar electronic database will be conducted. The review will include studies published from inception until May 25, 2020, reporting on the effect of vitamin K on CVD-related markers, especially coagulation factors and platelet activation in type 2 diabetes mellitus. Before the full-text screening, all studies will be screened by title, abstract, and keywords. The Downs and Black checklist will be used to assess the quality of the studies. Additionally, the Cochrane collaboration tool will also be used to evaluate the risk of bias across the included studies. Kappa Cohen's calculator will be used to assess the level of agreement between the authors.

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They current are planning aims to systematically explore and discuss the available evidence on the impact of vitamin K on the diabetes-cardiovascular disease (CVD)- correlated complications[.PROSPERO) registration number: CRD42020151667.[167].

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