MicroRNA 155, Factor XIII and Type 2 Diabetes Mellitus and Coronary Heart Disease

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Abstract

There is a rise in the number of individuals diagnosed with type 2 diabetes mellitus (T2DM) in South Africa. Cardiovascular disease is amongst the macrovascular complication of type 2 diabetes mellitus and accounts for the high mortality rate in patients with T2DM. The disease is characterized by insulin resistance and hyperglycaemia, which is also accompanied by oxidative stress, inflammation, hypofibrinolysis and hypercoagulation. Impairment of fibrinolysis and the hyperactivation of coagulation and the inflammatory pathways result in an increased risk of developing coronary heart disease. Factor XIII-A is one of the key coagulation factors that play a crucial role in the last stage of the coagulation cascade and it has been shown to play a critical role in the development of thrombotic diseases. In addition, there have been several studies done on the influence of FXIII-A polymorphisms on thrombotic diseases. The influence of genetic variations such as single nucleotide variants and gene expression regulators (micro-RNAs) are important factors involved in the hyperactivation of coagulation and hypofibrinolysis. Thus, this review aimed to summarise key aspects of coagulation, FXIII-A expression and potential FXIII-A genetic variations and epigenetic mediators (micro-RNA-155) in T2DM and patients with coronary artery disease.

Key words: FXIII-A, miRNA-155, Val34Leu, Coronary artery disease, Type 2 Diabetes Mellitus

Introduction

Coronary heart disease and type 2 diabetes mellitus

There is an increasing risk of coronary heart disease (CHD) associated with type 2 diabetes mellitus (T2DM) (1). The study by Ahmad *et al* (2015), found T2DM and fasting glucose (FG) closely associated with some of the mechanisms that lead to the development of CHD (1). They also found that a slight elevation of FG in non-diabetic individuals had an increased risk of developing CHD, which shows that glucose plays an important role in the association of T2DM and CHD progression (1). Factors that lead to patients with T2DM to developing CHD are increased blood glucose, smoking, low-density lipoprotein (LDL) cholesterol, body

mass index (BMI), inflammatory marker to name a few.

It is postulated that approximately one-third of the adult population will be diagnosed with hypertension by the year 2025 (2). Patients with CHD and stroke are diagnosed with hypertension (2). An enzyme that is associated with high-density lipoprotein (HDL) is paraoxonase-1 (PON1), it is calcium-dependent (3). The main function of PON1 is, that it induces oxidative stress and also leads to oxidative stress-related diseases such as some of the vascular diseases related to atherosclerosis (4). A link between hypertension, atherosclerosis and elevated levels of oxidative stress exists due to the disruption between antioxidant protection system and the reactive oxygen species (ROS) production (5, 6). Increased levels of free oxidative radicals are induced by lifestyle choices such as decreased physical activity, consumption of fast food and alcohol, smoking and stress that have been observed in patients with T2DM and CHD (2). PON1 is one of the enzymes that is involved in the removal of ROS (7).

There is a preventative role that PON1 plays in vascular diseases and the accumulation of oxidized lipids in LDL (8). This is done through the preservation of macrophage, HDL and LDL against the accumulation of oxidative stress and the end result of this is the suppression of the development of atherosclerosis (2). The enzyme also protects LDL against detoxification and oxidation of highly toxic compounds (9).

The risk of developing CHD is characterized by a combination of risk factor such as elevated blood pressure (BP), smoking, T2DM, obesity and family history of CHD (10). One of the medications used to control hypertension are calcium channel blockers (CCBs). Their mechanism of action is that they stop calcium, so that it does not enter the cells of the heart and arteries thus allowing the blood vessels to relax and dilate (11). C Türkeş *et al* (2022) found that the interaction between CCBs and PON1 resulted in the decreased level of the PON1 enzyme (12).

Elevated BP levels are associated with abnormal cholesterol levels and accompanied by increased BMI with an increase in prevalence of T2DM (10). In addition, coagulation factor fibrinogen is also one of the CHD risk factors, as elevated levels are also associated with T2DM, smoking and hypertension (10). A major cause of mortality and morbidity in T2DM is CHD (13).

One of the factors that links T2DM and CHD is obesity, the leading cause for both (14, 15). In a study done by Emdin *et al* (2017), they showed that there is a genetic predisposition to higher waist-to-hip ratio for BMI associated with elevated levels of risk factors such as blood lipids, insulin, glucose and systolic blood pressure, it is also associated with high risk of T2DM and CHD (16). They suggested that their results may indicate that body fat distribution could explain the variations between individuals and subpopulation in the risk of developing T2DM and CHD (16). One of the risk factors for CHD is increased levels of triglyceride-rich lipoproteins (17).

The pathophysiology and progression of T2DM is mainly mediated by factors such as inflammation, hyperglycaemia, hypercoagulation, hypofibrinolysis, insulin resistance, oxidative stress and formation of advanced glycation end-products (AGEs) (18). During the polyol pathway, the first enzyme that is involved is aldose reductase (AR), which converts glucose to sorbitol (19) by making use of NADPH (20). It is involved in the reduction of glucose and also associated in the pathophysiology of T2DM complication such as cataract, retinopathy, nephropathy, and neuropathy and thus this is a pharmaceutical target for treatment of T2DM complication (19) (20) (21). There is an increased risk of developing coagulopathies in T2DM patients due to the imbalance between clot formation and lysis resulting in hypercoagulation and hypofibrinolysis caused by hyperglycaemia (22).

One study has shown that elevated levels of blood glucose are able to induce the production of AGEs, oxidation of low-density lipoproteins, advanced oxidation of protein products that are associated with vascular injury observed in T2DM through underlying mechanisms which can lead to the development of atherosclerosis and can result in coronary heart diseases (23) .

Atherosclerosis is a chronic inflammatory disease of arteries that is due to endothelial injuries, platelet adhesion, macrophage and lipid accumulation (23). As glutathione reductase (GR), glutathione s-transferase (GST) and human PON1 are known to have a protective role against the increase levels of free radicals and a low level of these enzymes will result in accumulation of toxic substances that could lead to metabolic disorders (24). Several studies that have been done on inhibitors that could potentially inhibit PON1, found that sulfonamide which is a inhibitor used for antimicrobial drugs is able to inhibit the enzyme (25).

Hyperglycemia is able to alter the phenotype of vascular smooth muscle cells (VSMCs) from being contractile to being synthetic, which represents increased proliferation, extracellular matrix secretion and migration that contributes to mechanisms leading to heart diseases (23). Damage to the endothelial wall creates a site for platelet adhesion, which is then followed by changes in platelet shape, degranulation and platelet activation (26). The coagulation cascade plays an important role in the development of atherosclerosis observed in T2DM individuals and coagulation factor XIII-A is one of the factors that play such a role.

Structural composition of coagulation factor XIII-A

Fibrin and activated factor XIII play a key role in clot formation, any alteration in these two coagulation factors will results in either a hypercoagulable (excessive fibrin and factor XIII) or a hypocoagulable (reduced factor XIII and fibrin levels) state. Due to hyperglycemia seen in T2DM individuals, a hypercoagulable state is observed, and this contributes to the high mortality rate caused by thrombotic disease in T2DM patients (27). Hyperglycemia results in a hypercoagulable state through the activation of the plasminogen activator inhibitor-1 (PAI-1) via the transcription factor NF-κB which then results in the impairment of the tissue-plasminogen activator (tPA) leading to hypofibrinolysis (28). Factor XIII is a transglutaminase, which is composed of two subunits, A and two carrier B-subunits (FXIII-A2B2). During FXIII activation, its cleaved by thrombin, to separate the A and B-subunits (figure 1) (29).

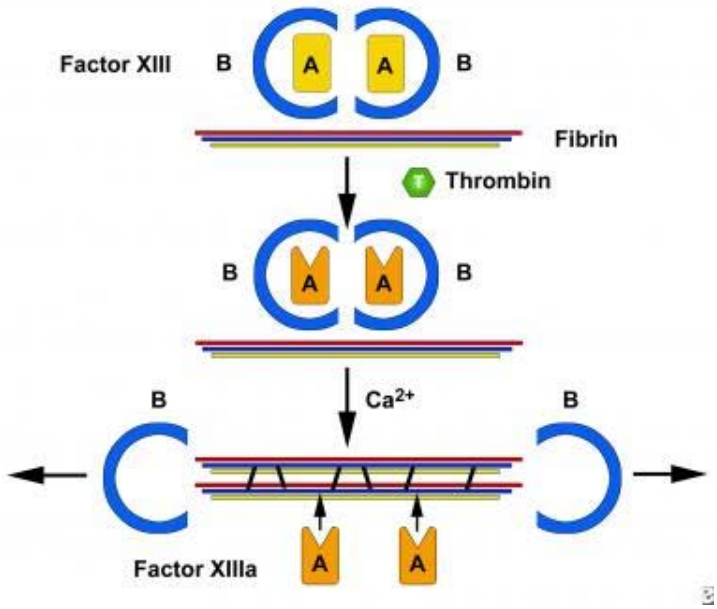

Figure 1: The activation of FXIII-A is done in the presence of thrombin which results in the dissociation of the B-subunits from the A. Reproduced from (30).

It plays a crucial role in the development of cardiovascular diseases and studies have demonstrated that factor XIII is involved in deep vein thrombosis due to its high expression levels (29). This factor is found in abundance in the α-granules of platelets, and is also found in megakaryocytes, monocytes and tissue macrophages (31). There are some studies that showed that elevated levels of FXIII-A was associated with high incidence of myocardial infarction and peripheral artery disease in female patients (32, 33).

Coagulation FXIII-A plays an important role in the cross-linking of the fibrin a and c chains and attaching the α2-plasmin inhibitor to fibrin using the e(c-glutamyl) lysyl isopeptide bonds (34). Through this, FXIII-A is able to enhance the strength of the fibrin clot and also protect it from being degraded (34). FXIII-A has different domains that play a significant role in how it interacts with other proteins in order to serve its function. It contains the following domains; the b-sandwich, catalytic core, ß-barrel 1 and 2 and the N-terminal activation peptide-FXIII (AP-FXIII) (34). The FXIII- A subunit (figure 2) consists of 732 amino acids (aa), where the ß -sandwich contains 38-184 aa, catalytic core contains 185-515 aa, ß -barrel 1 contains 516-628 aa, ß-barrel 2 contains 629-731 aa and AP-FXIII contains 1-37 aa (35). The AP-FXIII covers the catalytic site of FXIII-A at the Cys314 (35).

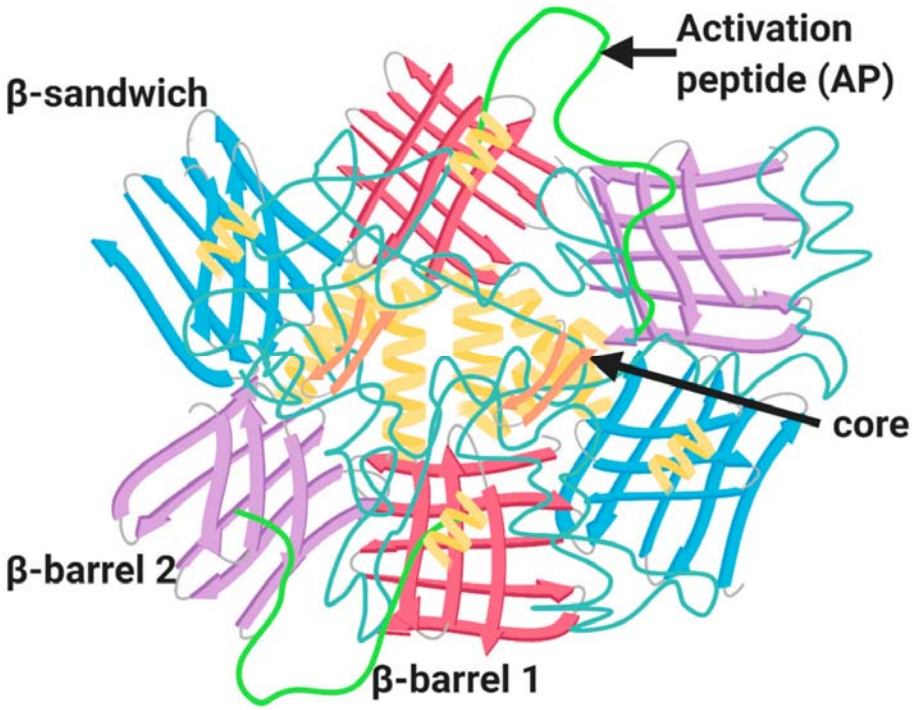

Figure 2: Amino acid structure of FXIII-A, illustrating the different domains and activation sites. (36)

The ß -barrel 1 and 2 of the A subunit is the one responsible for the binding of the A subunit binding to the B subunit (37). The AP-FXIII domain has many roles such as in the stability of FXIII-A, in the regulation of FXIII-A activity by covering the active site and also plays a role in the activation of FXIII-A as freely released AP-FXIII is able to decrease FXIII-A activation (38). Activation of FXIII-A occurs when the following events take place; the AP-FXIII is cleaved by thrombin, the B subunit is separated from the A subunit and ca $^{2+}$ binds to FXIII-A (38). The above mentioned events enable the exposure of fibrinogen α chain recognition site on FXIII-A for fibrin cross-linking (39). From the above mentioned, any structural alterations can result in the dysfunction of the factor and genetic alterations such as single nucleotide variants (SNVs) are able to affect the function of the factor.

Genetic alterations to coagulation factor XIII-A

In addition to hyperglycemia, oxidative stress, inflammation and genetics also plays a role in the progression of the pathogenesis of T2DM. Aldose reductase is known to be a multi-disease pharmaceutical target for the treatment of T2DM complications and inflammation. Recent studies that have shown that submicromolar inhibitors such as pyridazinone can be used as inhibitors for AR (40). Another study found that 5-(arylidene)thiazolidine-2,4-diones was a more potent inhibitor for AR and can be used for the treatment and management of T2DM complications and other nondiabetic related diseases (41). Study done by Sever *et al* (2021) showed that a compound that was synthesized with a 1,3-diaryl-5-(4-fluorophenyl)-2-pyrazoline moiety was able to also act as an inhibitor for AR (42).

There are genetic variations that are found in the human genome, variations such as inversions, substitutions, copy number variations and SNVs. Most commonly found variations are SNVs and most of them have no measurable outcomes in medical conditions, however, there are some which are able to influence the susceptibility of a disease (43). Variants are able to affect the coding of the amino acid sequence of a protein if present in the exon and as a result, alters protein structure and function (44).

Several studies have demonstrated that some genetic variations in genes code for proteins that influence coagulation. Thrombophilic gene variants include factor V Leiden (rs6025), prothrombin gene G20210A (rs1799963), fibrinogen gamma 10034>T (rs2066865) and FXIII-

A Val34Leu located on exon 2 c.103 G>T (rs5985) (44). Other FXIII subunit-A SNVs include Tyr204Phe located on exon 5 (rs3024477) and Pro564Leu (rs5982) located on exon 8 (45). Not all factor XIII-A variants are associated with hypercoagulation, but some are involved in hypocoagulation which influences haemorrhagic diseases. A study done by Anwar *et al* (1998) demonstrated that genetic variants that occur affect the stability of FXIII-A, such as the Asn541Lys variants located in exon 12 and was found to play an important role in stabilizing a turn and that destabilization of the turn resulted in misfolding of FXIII-A (46).

Most of these SNVs are missense mutations and influence the function of FXIII-A. Thestudy done by de Lang *et al* (2006) investigated six SNVs (Val34Leu, Tyr204Phe, Pro564Leu, Val651Ile (rs5987), Glu625Gln (rs5988) and -246G>A ((rs1024231) in the promoter region SNV) in FXIII-A that affect the functionality of the factor in 201 dizygotic (DZ) twins (47). The study found a significant association between SNVs -246G>A, Val34Leu, Tyr204Phe and Pro565Leu and the activity level of FXIII-A (47). Another FXIII-A missense SNV that affects the stability of FXIII-A is Val415Phe located on exon 3 c.1243 G>T on the core domain (rs121913070) and the variant alters conformational changes that could lead to the stability of FXIII-A (48-50). Other SNVs such as Met243Thr (rs267606788) affect the correct positioning of the activation peptide on FXIII-A (51). The Asn61Lys (rs121913067) located in the β-sandwich results in a change in the polarity where a polar charge amino acid is replaced by a uncharged amino acid (52). The most commonly investigated FXIII-A functional SNVs are Val34Leu, Tyr204Phe and Pro565Leu. In a meta-analysis study done by Jung *et al* (2017), studies done worldwide on the Val34Leu SNV and association with coronary artery disease (CAD) were done on 25 European, 6 North American, 3 Asian, 1 South American and 1 African populations (53). Many of the missense SNVs occur in the core catalytic domain of FXIII-A (50).

The Val34Leu SNV is the most common studies FXIII-A variant due to its location 3 aa away from the thrombin cleavage site (54). Individuals that carry the 34Leu genotype are found to produce thick fibrin fibers in conditions of high levels of fibrinogen (54). The Pro564Leu SNV is located on the ß -barrel 1 domain of FXIII-A plays a role in the interaction of the A and B subunits and affects how much FXIII-A is activated (55). How different variants in the same gene interact with each other plays a key role in the development of various genetic associated diseases (55). The interaction of FXIII-A variants Val34Leu and Pro564Leu has been studied in ischemic stroke, hemorrhagic stroke and myocardial infarction (56, 57). Results have shown

that these 2 variants are linked to the development of thrombotic diseases (54). On the other hand, the Val34Leu SNV has also been showed to have a protective effect against thrombotic diseases (54). In addition, epigenetic regulation of FXIII-A plays a role in the development of atherosclerosis.

Epigenetic regulation

An important mechanism of the epigenetic control of cellular processes occurs through microRNA (miRNA) expression. These miRNAs are small, non-coding, single-stranded RNA products that consists of 17 to 25 nucleotides (58). MicroRNA regulates gene expression through messenger RNA (mRNA) degradation, thereby blocking mRNA translation (58). MicroRNAs play a role in the susceptibility and progression of a number of diseases including cardiovascular disease (23). miRNAs have been found to be involved in coronary heart diseases through either overexpression or under expression of certain genes, which result in the alteration of proteins synthesis. If genetic variants are present in the sequence of miRNA genes or the 3′ untranslated region (UTR) of the miRNA target genes, miRNA facilitated regulation of the target genes is disrupted (58). Main function of miRNAs is regulation of gene expression and there is a lot of miRNA which target multiple mRNA transcripts. They are also involved in cellular proliferation regulation such as platelets. reference

MicroRNAs have been shown to be contained in apoptotic bodies (59). Each miRNA has a specific cluster of genes that it regulates (59). Where certain miRNAs have been shown to be involved in the regulation of glucose metabolism (60), insulin signaling (61) and the development of T2DM to name a few (62).

MiR-155

There are some miRNA that are involved in the stimulation of immune cells and miRNA such as miR-155, which has been shown to play a key role in the differentiation of T-helper cells (63). This miRNA has been associated with diseases such as atherosclerosis and autoimmune inflammation (63). In immune cells such macrophages, miR-155 is highly expressed during the inflammatory response (63). Furthermore miR-155 in macrophages is involved in the regulation of other miRNAs, where it induces the expression of miR-99-5p, miR-143-3p and miR-147-3p, while it inhibits the expression of miR-582-3p and miR-709, thus, this miRNA can serve as a stimulator or inhibitor for other miRNA expression (63). miR-155 also plays a key role in the differentiation of brown fat tissue (63).

There are not only pathophysiological factors that affect the progression of T2DM, but there are also epigenetic factors such as miRNAs that take part. These miRNAs are able to target several genes that are involved in cell proliferation, differentiation and apoptosis and it has been shown that any dysfunction in miRNAs is able to alter different pathways in T2DM complications (64). Hyperglycemia causing platelet, macrophage and endothelial cell dysfunction is able to alter the expression of miRNAs and this has been shown in vivo and in vitro studies (64). Elevated miR-155 in macrophages causes them to produce pro-inflammatory cytokines, and the miRNA targets anti-inflammatory genes and stabilizes TNF-α (65). In adipocytes the miRNA induces the release of cytokines (66).

MiRNAs are transcribed from either the exonic or intronic region of gene and miRNAs such as miR-155, miR-22 and miR-146a are transcribed from the exonic region (67). The expression of miRNAs occurs due to different stimulations, for example miR-155-5p and miR-155-3p are expressed in response to the immune system by the B cells and their genes are found within the Integration Cluster gene (BIC) (67). Other factor miRNA stimulations are stress and steroid hormones and these stimuli affect the expression of miRNAs (67).

There are several levels where the expression of miRNAs can be regulated, for example they can be regulated at transcriptional and post-transcriptional levels (67). Regulation of miRNA expression at the transcriptional level involves the alterations of intragenic miRNAs or intergenic miRNAs (67). Intergenic miRNA have their own promoters, they are controlled by separate transcription factors and they are expressed independently (67). Both expression of intragenic and intergenic miRNAs can be altered by mutations or methylation of the promoters (67). The post-transcriptional level regulation occurs due to low expression of miRNAs caused by alterations in the activity of important miRNA biogenesis enzymes, for example Dicer and Drosha, where the activity of these enzyme is altered by epigenetic modifications or mutations (67). Besides genetic factors, miRNA expression can be affected by endogenous compounds (hormones and cytokines) or exogenous compounds (67).

Development of atherosclerosis and miR-155 multi-targets

The development and progression of atherosclerosis not only depends on pathophysiological factors such as inflammation and coagulation factors, but miRNAs are also involved. In response to shear stress, endothelial cells increase the expression of miR-21 (68). While miR-

155 has been suggested to protect the endothelium through lowering the expression of endothelin-1 and angiotensin II type I receptor (69). The miRNA also plays a role in the inhibition of VSMC differentiation through the decrease of angiotensin II type I receptor expression (70). The secretion of T-cell cytokines and chemokines are essential during the development of the atherosclerotic plaque and miR-155 targets cytokines secreted by CD4+ T cells (71). In addition, miR-155 is required for the survival of T regulatory cells, T-helper 17 response, the activation and function of dendritic cells (72, 73). Differentiation of macrophages into M1 or M2 phenotype is also influenced by miRNAs, where increased expression of miR-155-5p, -181a, -204-5p and -451 and decreased expression of miR-125-5p, -143-3p, -145-5p and -146a is found in M1 macrophages compared to M2 macrophages (74). There is an increased expression of miRNAs such as miR-21, -146a, miR-125a-5p, -146a, -146b-5p and -155 in the transition of monocytes to macrophages and also the formation of foam cells (75).

In a study done by Chen *et al* (2009) they found that if differentiated macrophages are treated with oxLDL to induce the formation of foam cells, there is an elevation in the expression of miR-125a-5p, -146a, -146b-5p and -155 (76). In contrast, miR-155 acts as a negative feedback regulator, where it is able to decrease inflammatory response and lipid uptake via scavenger receptors (77). A study done by Fichtlscherer *et al* (2010) showed that CAD patients had elevated levels of miR-133 and -208a, while there was a decrease in miR-17, -92a, -126, -145 and -155 (78). Another study done by Marques *et al* (2016) that investigated 84 miRNAs associated with CAD found that only 10 miRNAs (let-7a, let-7c, let-7e, miR-23b-3p, miR-107, miR-155, miR-181a, miR-181b, and miR-320a) were upregulated in patients with heart failure and miR-155 expression levels were elevated by 6.67 fold change ($p=0.002$) (79).

Macrovascular complications in T2DM results in accelerated development of atherosclerosis that leads to ischaemic heart disease (80). It has been suggested that T2DM can alter the function and expression of miRNAs, thus miRNAs can be used as novel biomarkers of T2DM (81). These miRNAs were identified in a meta-analysis study where 40 miRNAs were dysregulated in T2DM and the following were found to be biomarkers of T2DM (miR-29a, -34a, -375, -103, -107, -132, -142-3p and -144) (82). The miR-155 has been suggested to play a role in the pathogenesis of T2DM related complications (83). It was seen in a study by Khamaneh *et al* (2015), where they found that expression of miR-155 was downregulated in diabetic kidney, heart, aorta, peripheral blood mononuclear cell and sciatic nerve (83). Another study done by Huang *et al* (2014), found that hyperglycemia results in elevated levels of miR-

155 and miR-146a in renal glomerular endothelial cells and TNF-α, transforming growth factor- β1 (TGF-β1) and nuclear factor-κB (NF-κB) were highly expressed (84).

Another factor that contributes to the pathogenesis of atherosclerosis is decreased levels of endothelial nitric oxide synthase (eNOS) (85). Factors such as estrogen and shear stress are able to increase the expression of eNOS (86, 87). On the other hand, inflammatory activators such as lipopolysaccharide (LPS), TNF-α, oxLDL and ROS inhibit the expression of eNOS (85). In a study done by Lee *et al* (2014) they showed that expression of eNOS was negatively controlled by miR-155 through NF-κB which is an inflammatory activator and induces the expression of TNF-α (88). The miRNA binds directly to the 3´UTR of eNOS mRNA, which leads to reduction of miRNA expression and expression (88). Choi *et al* (2017) demonstrated that carbon monoxide (CO) and bilirubin attenuated TNF-α mediated miR-155 synthesis through the suppression of the canonical NF-κB pathway, which then restores eNOS expression (85). Thus, this shows that miR-155 regulates many processes and pathways in the development of different diseases and this is summarized in figure 3.

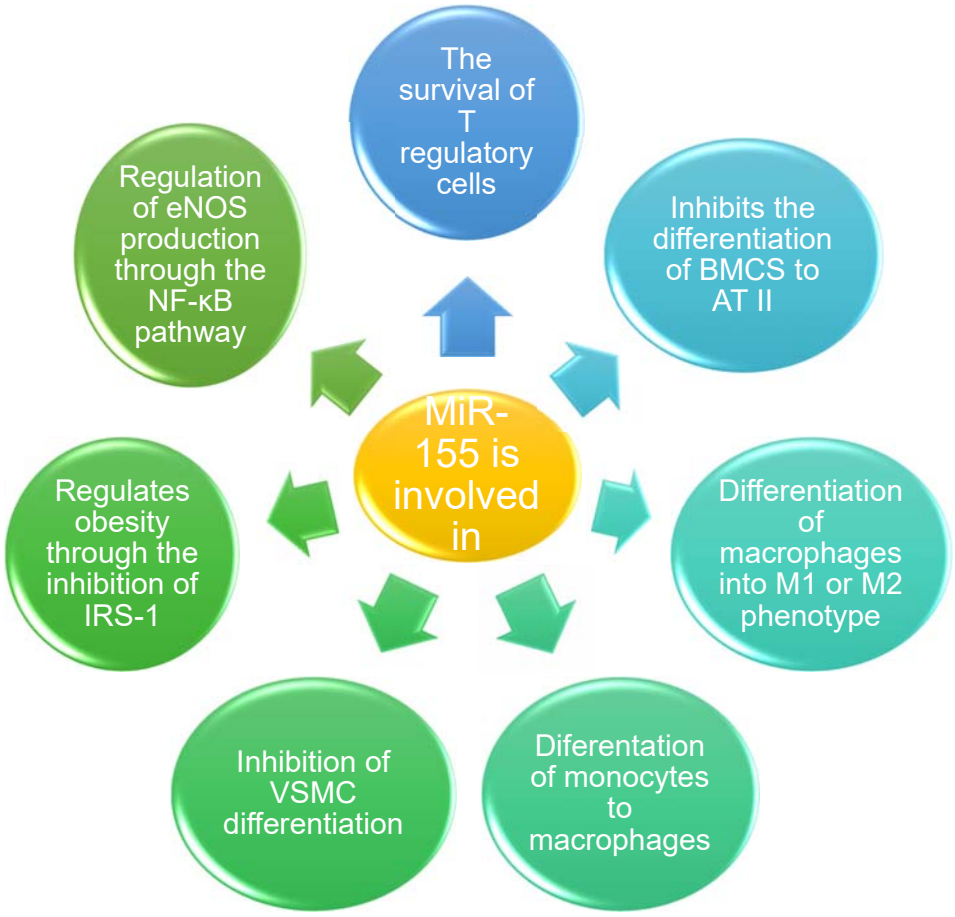

Figure 3: A summary of processed miR-155 is involved in regulating.

MiR-155 and obesity

Obesity is one of the characteristics of T2DM. MiRNAs such as miR-155 has been suggested to be involved in the regulation of obesity (89). It is suggested that it has a protective effect against obesity, where it controls the signaling pathways leading to obesity such as browning, adipogenic and the inflammatory pathways (89). This is done through miR-155 regulating the transformation of adipocytes into white rather than brown phenotype (89). It also regulates lipolysis, that may influence energy storage in adipocytes (66). Lastly it affects adipose tissue accumulation through the regulation of inflammation by the activation of pro-inflammatory pathway (65, 89).

In a study done by Gaudet *et al* (2016), knocking out miR-155 in female mice resulted in no weight gain when the mice were fed a high fat diet, thus suppression or inhibition of the miRNA protects against obesity (89). They suggested that this can be due to processes such as insulin sensitivity, free fatty acid release and the availability of hormones involved in obesity are also affected during miR-155 knockout process (89). Elevated levels of miR-155 have been associated with inhibition of the Insulin receptor substrate 1 (IRS-1) , which decreases the transformation of adipocytes (90, 91). And as a result, this leads to hyperinsulinemia and insulin resistances due to miR-155 targeting TNF-α affecting insulin sensitivity (92).

New miR-155 targets

From the above mentioned, miR-155 has been shown to be involved in various pathways. Using the Target Scan we have identified that FXIII-A is another target for this miRNA and shown below (figure 4) is the region of the FXIII-A gene to which miR-155-5p binds to and the binding site is highly conserved. It binds at the 229-235 position of the 3´UTR and regulated FXIII-A post-transcriptionally as shown in figure. However, the mechanism of which the miRNA regulates the coagulation factor is not known and more studies have to be done.

	Predicted consequential pairing of target region (top) and miRNA (bottom)	Site type	Context ++ score	Context++ score percentile	Weighted context ++ score	Conserved branch length	P_{CT}
Position 229-235 of F13A1 3' UTR hsa-miR-155-5p	5' ...UUCCAAAGAGUGCUAAGCAUUAG... ||||||| 3' UGGGGAUAGUGCUAAUCGUAAUU	7mer-m8	-0.06	55	-0.06	3.139	0.23

Figure 4: This is the 3´UTR binding site of has-miR-155-5p on FXIII-A, at position 229-235 (From TargetScanHuman) (93).

Conclusion

The development and progression of T2DM and CHD is affected by several factors and these factors are interlinked in such a way that the development of CHD in T2DM individuals is exacerbated by those factors. There have been several biomarkers of T2DM and CHD that have been discovered by different studies and the role of genetic biomarkers such as SNVs and miRNAs have been found over the years. Missense variants that affect coagulation factor XIII-A play an important role in the development of coagulopathies such as the development of atherosclerosis. In addition, post-transcriptional regulator such as miR-155 also plays an important role in the development of atherosclerosis. Thus, the unregulated expression of FXIII-A by the presence of SNVs and the post-transcriptional regulation of FXIII-A may play a key role in the coagulopathies seen in T2DM and CHD individuals.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

FUNDING

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CONFLICT OF INTEREST

No conflict of interest for this study.

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